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**(Through proper channel)**

**Subject: -** Thesis's Submission

Respected Sir,

I have joined the Department of Pediatric Surgery as Senior Resident in July 2021. I am enclosing my thesis titled **"Clinico - Epidemiological Profile of Disorders of Sex Development Presenting to A Tertiairy Care Center: A Descriptive Observational Study"** in partial fulfillment of the requirement for degree of Master of chirurgiae (M.Ch) (Pediatric Surgery).

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# CLINICO-EPIDEMIOLOGICAL PROFILE OF DISORDERS OF SEX DEVELOPMENT PRESENTING TO A TERTIARY CARE CENTER: A DESCRIPTIVE OBSERVATIONAL STUDY

**THE THESIS SUBMITTED TO THE FACULTY OF**

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

**FOR THE AWARD OF THE DEGREE MCh IN THE SUBJECT OF**
**PEDIATRIC SURGERY**

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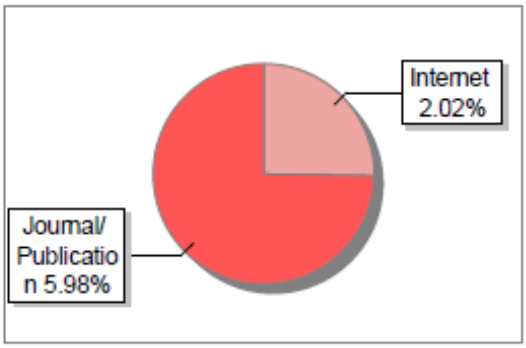


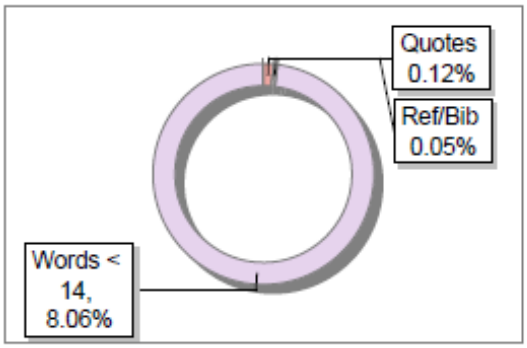


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## ACKNOWLEDGEMENT

In the course of this intellectually stimulating and pedagogically enlightening endeavor, I have acquired a profound reservoir of knowledge and experience. As the culmination of this work approaches fruition, I reflect upon the entire journey and acknowledge the substantial support and blessings bestowed upon it by numerous individuals. It is my solemn obligation to extend my heartfelt gratitude to those who consistently served as fountains of inspiration throughout the entire research process.

I find myself at a loss for words when attempting to articulate the extent of my indebtedness to my esteemed mentor, Dr. Pramod K Sharma. His remarkable foresight, pragmatic approach, and comprehensive mastery of the subject matter have provided the guiding impetus behind all my endeavors in shaping this project. Dr. Sharma's unfailing willingness to dedicate his invaluable time to resolving the myriad inquiries and uncertainties that arose during the study has been instrumental in shaping this thesis and fostering my intellectual growth.

I must also express my profound appreciation to my co-guide, Dr. Roshan Chanchlani, whose erudition and sagacious guidance were indispensable in bringing this work to fruition.

I extend my gratitude to Dr. Mahesh Maheshwari, my co-guide, for his collaboration, insights, and unwavering encouragement from the project's inception, which significantly contributed to its successful completion.

I wish to acknowledge and thank my esteemed consultants, Dr. Reyaz Ahmad (Additional Professor), Dr. Amit Gupta (Associate Professor), Dr. Suresh K Thanneeru (Assistant Professor), and Dr. Vidhya Gunasekaran (Assistant Professor), as well as my colleagues, Dr. Ankit Kasundra, Dr. Abhilash Sahu, Dr. Priyesh Sankar, Dr. Lokesh Purohit, Dr.Salman, Dr.Rashmi, and Dr.Vineet, for their invaluable advice and assistance, particularly in patient recruitment. I thank Dr. Prashant (PSM) for his technical data compilation and analysis support.

I want to thank our nursing and supporting staff, Ranu and Hemanti, for their cooperation in guiding patients.

I want to thank the patients and their families, without whom this study would not have seen the light of day.

For all that I am cognizant of their contributions and the countless sacrifices made, I express my gratitude to my parents, the late Shri Ramadhar R Pandre and Mrs. Laxmi Bai Pandre, and my wife, Dr. Varsha, for their unwavering support during moments of uncertainty and their unconditional love.

Lastly, I offer my gratitude to the Divine for granting me the courage to complete this work. I beseech for the serenity to accept the things beyond my control, the fortitude to effect change where possible, and the wisdom to distinguish between the two.

**ABSTRACT**

**Introduction:-** Disorder of sex development (DSD) is a rare congenital condition in which atypical development of internal and/or external genital structures occur. There is no consensus amongst clinicians yet about who should be investigated for DSD. There is no available data on the epidemiological profile of DSD from central India. The aim of this study is to identify the incidence of DSD in central India and identify which type of DSD is most prevalent. This study will provide data for further planning, improvement in medical and health services for the management of DSDs.

**Aim and objectives:-** To study the relative incidence of various types of DSDs presented to AIIMS Bhopal and its comparison with data from other regions.

**Methods:-**It is a hospital-based Clinico-epidemiological study, Patients included in this study were worked up for DSDs as per the prevailing protocol. Hypospadias with undescended testis, Hypospadias with bifid scrotum, Proximal penile hypospadias, Micropenis, Bilateral Female inguinal hernia, Bilateral Undescended testis, Clitoromegaly were included.

**Results:- In this study** 40 patients were enrolled in this study according to inclusion criteria. Out of 40 patients, 17 patients presented with proximal penile hypospadias and bifid scrotum, nine patients had hypospadias with UDT, seven patients presented with bilateral female inguinal hernia, three had bilateral UDT, three were Micropenis, two were mega clitoris and one had bilateral UDT with Micropenis.

We observed that the patients who presented with proximal penile hypospadias and UDT had various types of DSDs.In these patients steroidal synthesis defects was most commonly seen followed by mixed gonadal dysgenesis, and SRY translocation.In three patients presenting with Micropenis steroidal synthesis defect and Congenital Adrenal Hyperplasia was commonly seen. This study showed a 35% positivity rate, with a high incidence of steroidal synthesis defect followed by Congenital Adrenal Hyperplasia.

**Conclusion:-** This study sheds light on the prevalence of Disorders of Sex Development (DSDs) in central India, offering valuable insights for guiding future research endeavors and establishing diagnostic protocols for such patient populations.

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## APPENDIX 3-LIST OF ABBREVIATIONS

| | |
|---|---|
| DSD | Disorders of Sex Development |
| AMH | Anti-Mullerian Hormone |
| AIS | Androgen Insensitivity Syndrome |
| CAH | Congenital Adrenal Hyperplasia |
| PESLW | Lawson Wilkins Pediatric Endocrine Society |
| ESPE | European Society for Paediatric Endocrinology |
| LH | Luteinizing Hormone |
| GMD | Mixed Gonadal Dysgenesis |
| WT | Wilms tumor |
| SF | Steroidogenic Factor |
| INSL3 | Insulin-Like factor-3 |
| DNA | Deoxy Nucleic Acid |
| RNA | Reboxy Nucleic Acid |
| FISH | Fluorescence In Situ Hybridization |
| IQR | Inter Quartile Range |
| 5α-RD | 5α-Reductase type-2 Deficiency |
| ICH-GCP | International Conference on Harmonization Good Clinical Practice |
| hCG | human Chorionic Gonadotropin |

| | |
|---|---|
| CAIS | Complete Androgen Insensitivity Syndrome |
| T | Testosterone |
| DHT | Dihydrotestosterone |
| 17β-HSD3 | 17β-Hydroxysteroid Dehydrogenase type-3 |
| FSH | Follicle-Stimulating Hormone |
| 17-OHP | 17-HydroxyProgesterone |
| B/L | Bilateral |
| UDT | Undescended Testis |
| NVD | Normal Vaginal Delivery |
| LSCS | Lower Section Caesarean Section |
| NICU | Neonatal Intensive Care Unite |
| BP | Blood Pressure |
| SD | Standard Deviation |
| HR | Heart Rate |
| PAIS | Partial Androgen Insensitivity Syndrome |
| GD | Gonadal Dysgenesis |

# INTRODUCTION

An individual's biological sex arises from the intricate interplay of internal ductal structures and external genitalia, a differentiation orchestrated by the influence of sex-determining genetic factors and hormones produced by specialized gonadal tissues.[1] However, in certain instances, determining sex solely based on outward appearance becomes challenging. Instead of employing potentially confusing or stigmatizing terminology such as "ambiguous genitalia," "intersex," "hermaphroditism," or "pseudo-hermaphroditism," a more encompassing classification known as "Disorders of Sex Development (DSD)" has been introduced. This term pertains to congenital conditions where the typical development of gonadal, chromosomal, or anatomical sex deviates from the norm.[2] Nevertheless, it is essential to acknowledge that some individuals may perceive negative connotations associated with the term "disorder" and its implications involving sexual behavior.[3] Estimating the incidence of DSD poses a significant challenge, with approximations suggesting a prevalence of roughly 1 in 4,500–5,500 newborns.[4] Moreover, the occurrence of individuals with 46, XY chromosomal composition and DSD is estimated at 1 in 20,000 births, while the global incidence of individuals with 46, XX chromosomes and DSD ranges from 1 in 14,000 to 15,000 live births, with regional variations.[5]

Biological sex is dictated by the interplay of genetic factors and hormonal influences. Distinct manifestations of sexual developmental anomalies may become apparent at various stages of an individual's life. DSD can occasionally be integral to a broader genetic syndrome.[6,7]

The field of research on Disorders of Sex Development (DSD) has been predominantly directed toward the discernment of genetic alterations responsible for inducing aberrant sexual development, employing a diverse array of investigative methodologies. Nevertheless, it is worth noting that approximately 50% of instances have hitherto yielded a well-defined etiological basis through comprehensive techniques encompassing sequencing, deletion, and duplication analyses. This diagnostic shortfall may be ascribed to an incomplete understanding of the pathogenesis and underlying mechanistic underpinnings of DSD, inherent disparities in assessment techniques and phenotypic characterization, as well as a somewhat limited acknowledgment of the pivotal role of molecular genetic diagnostics in directing the management and therapeutic interventions for affected individuals.[8]

Sex chromosomes play a pivotal role in dictating the differentiation of gonads, ultimately determining the phenotypic expression of sex. Within the urogenital ridge, the same anatomical structures give rise to the distinct male and female gonads and genitalia. Testosterone is a key factor in promoting the differentiation of Wolffian ducts, while anti-Mullerian hormone (AMH) orchestrates the regression of Mullerian ducts. Anomalies in this process can lead to the emergence of genital ambiguity. Notably, in males, AMH is the crucial regulator responsible for Mullerian duct regression. Androgen insensitivity syndrome (AIS) manifests as a spectrum of conditions characterized by varying degrees of defective masculinization in individuals possessing a 46, XY chromosomal complement.[9,10]

The initiation of sexual differentiation is primarily contingent on chromosomal sex, a determination set at the moment of fertilization, with consequential ramifications for gonadal differentiation, which, in turn, dictates the development of both internal and external genitalia, collectively referred to as the phenotypic sex. Specifically, testosterone plays a decisive role in instigating the differentiation of the Wolffian ducts, while AMH is pivotal in promoting the regression of Mullerian ducts in males. Disruptions in this intricate pathway can precipitate genital ambiguity. It is pertinent to note that Mullerian duct remnants are frequently encountered in 46, XY DSD and 46, XY gonadal dysgenesis cases. AIS represents a group of conditions arising from defects in the androgen receptor, culminating in a spectrum of outcomes pertaining to defective masculinization in 46 XY individuals.[11,12]

Disorders of Sex Development (DSD) affect the development of chromosomal, gonadal, or anatomical sex. Causes include early antenatal exposure to androgen[13], foetal aromatase deficiency[14], maternal androgen-producing tumours[15], maternal exogenous androgen exposure[16,17], Wnt-4 mutation[18], or associations. Most common cause of 46, XX DSD is virilizing congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency[19].

Individuals with DSD can have varying degrees of ambiguity in their external genitalia. Patients with Ovo testicular DSD have both ovarian and testicular tissues, while those with gonadal dysgenesis present with a female phenotype but a 46, XY karyotype. [20] Mutations in the SRY gene account for 10–20% of cases. Gonadal neoplasms occur in 25–55% of patients, usually after puberty.[21] Mixed gonadal dysgenesis involves one

gonad being more developed, usually as an immature ovary or testis, while the other is a streak structure[22], with variable definitions among authors based on karyotype and degree of asymmetrical gonadal differentiation.[23]

There has yet to be a consensus among clinicians on who should be investigated for DSDs. Moreover, there needs to be available data on the epidemiological profile of DSD in central India[24-28] Therefore, this study aims to identify the incidence of DSD in central India and determine which type of DSD is most prevalent. The outcome of this study will aid in planning to improve medical and health services for managing DSDs.

# REVIEW OF LITERATURE

DSD, or Disorder of Sex Development, is a developmental anomaly characterized by atypical determination and/or differentiation of chromosomal, gonadal, and phenotypic sex[29]. The term 'DSD' was officially defined during the Chicago Consensus of 2006 and is used to describe a congenital condition wherein the development of chromosomal, gonadal, and anatomical sex follows an atypical trajectory.[2] This nomenclature promotes accuracy within the medical community while avoiding potential confusion with other conditions such as transgenderism, gender dysphoria, or homosexuality. However, the term 'disorder' may be perceived negatively by some patients, and there can be misconceptions about the term 'sex,' which is often mistakenly linked to sexual behaviour.[3]

Determining a clinical classification for DSD can be challenging due to the striking similarities in physical characteristics among those affected, alongside the potential involvement of multiple causative factors.[29-30] As a result, there needs to be a clear definition to avoid uncertainty in estimating the incidence of DSD conditions. However, individual estimates suggest an incidence rate of approximately 1 in 4,500 to 5,500 newborns.[31] This encompasses many congenital genital anomalies, including cryptorchidism and hypospadias, which can occur in 1 in 200 to 1 in 300 births.[31] Additionally, the incidence of DSD in 46 XY individuals is estimated to be 1 in 20,000 births.

In contrast, the global incidence in 46, XX individuals, predominantly attributed to congenital adrenal hyperplasia, is 1 in 14,000 to 15,000 live births.[5] Regional variations arise due to disparities in the prevalence of pathogenic genetic variants. Notably, congenital adrenal hyperplasia and mixed gonadal dysgenesis comprise a significant proportion of DSD cases, often clinically manifesting as genital ambiguity. [8]

At the moment of fertilization, chromosomal sex is determined, which plays a critical role in the development of genital structures. The gonads' differentiation, in turn, influences the development of both internal and external genitalia, collectively referred to as phenotypic sex. Interestingly, the male and female gonadal and genital structures arise from identical precursor tissues on the urogenital ridge. From the yolk sac, primordial germ cells migrate toward the urogenital sinus in approximately the fourth week of gestation. The cells that serve as precursors for granulosa-theca or Sertoli-Leydig cells are also located within the urogenital ridge. [9]

During embryonic development, certain genes such as SRY, SOX9, SF1, and WT1 need to be expressed for indifferent gonads to differentiate into testes. [10] Around the sixth week of development, the Mullerian ducts appear next to the Wolffian ducts. The regression of the Mullerian ducts is facilitated by anti-Mullerian hormone (AMH), which is secreted by Sertoli cells within the testes. If not regressed, the Mullerian ducts would develop into the fallopian tubes, uterus, and upper part of the vagina. On the other hand, the differentiation of Wolffian ducts is driven by testosterone, which is produced by Leydig cells in the testes. Eventually, the Wolffian ducts form the vas deferens, epididymis, and seminal vesicles.[11]

Most of the Mullerian duct in males degenerates during fetal development, except for two remaining parts. The cephalad end remains as the appendix testis, while the caudal end endures as the prostatic utricle.[12] The masculinization of external genitalia depends on the conversion of testosterone to dihydrotestosterone, which is facilitated by the enzyme 5α reductase. The level of masculinization is determined by the amount of fetal androgens present and the response of the tissues to these androgens. Any abnormalities in this complex pathway can lead to genital ambiguity, resulting in under-virilization of an XY individual, over-virilization of an XX individual, or, in rare cases, disturbances in gonadal differentiation. During male embryonic development, the Mullerian ducts are supposed to regress, regulated by a hormone called AMH.[32]

However, in some cases, the Mullerian ducts do not properly regress due to insufficient synthesis and/or action of AMH[25,33], leading to their remnants in male individuals. This situation is commonly observed in 46, XY DSD[34], and 46, XY gonadal dysgenesis[35,36]. Additionally, Androgen Insensitivity Syndrome (AIS) is a condition that affects the androgen receptor and can result in varying degrees of defective masculinization in 46 XY individuals. The AIS phenotype can also be complicated by the presence of somatic mosaicism for mutations in the AR gene[37]. In some cases of AIS with 46, XY DSD, remnants of the Mullerian ducts can also be present.[38-40]

Somatic sex development involves three key components: chromosomal sex, which is determined by the combination of X and Y chromosomes; gonadal sex, which is represented by the presence of testes and/or ovaries; and anatomic sex, which pertains to the development of external and internal genitalia in males and/or females. This complex

process of sex development involves two sequential phases, each of which is orchestrated by distinct mechanisms.[41]

At five weeks post-conception, human embryos are uniform and have the potential to differentiate into either male or female anatomical structures. This indicates a common starting point for all individuals. Sex determination begins around the sixth week of development, where sex chromosomes (XX or XY) play a crucial role in directing bipotential gonads toward the development of testes or ovaries. The presence of the SRY gene on the Y chromosome initiates a complex cascade of genetic signalling events that finally leads to the formation of testes. Previously, it was believed that ovaries were developed without the Y chromosome and SRY. However, recent research suggests that ovarian development is an active process that requires the activation of specific genes conducive to ovarian development and concurrent interference with testicular development. Deviation from the typical sex determination pathway can lead to atypical sexual anatomy, often accompanied by an elevated risk of gonadal cancer, inadequate production of sex hormones to initiate spontaneous puberty or maintain secondary sexual characteristics, and potential infertility.[42-44]

During the process of sex development, a crucial phase called sex differentiation takes place. This phase involves the maturation of internal genital ducts and external genitalia. The production of anti-Müllerian hormone (AMH) by testicles plays a significant role in suppressing the development of Müllerian structures, which act as precursors to the fallopian tubes, uterus, and upper two-thirds of the vagina. When an ovary emerges from the bipotential gonad, and there is no AMH present, the differentiation of female-typical internal structures begins under the regulation of multiple genes. Additionally, the testes produce testosterone, which is responsible for the differentiation of Wolffian structures and the development of the epididymides, vasa deferentia, and seminal vesicles.[41]

While the internal genitalia are characterized by the Wolffian and Müllerian ducts, which have a bipartite nature, the external genitalia originate from a single undifferentiated precursor. The characteristic appearance of the penis and scrotum is shaped by the conversion of testicular testosterone into dihydrotestosterone. However, if testosterone is absent or androgen action at the target tissues is compromised, the genital

tubercle will develop into the clitoris, the urethral folds will give rise to the labia minora, and the labioscrotal swellings will form the labia majora.[41]

The onset of puberty marks the end of sexual development and is characterized by the appearance of secondary sexual characteristics, a growth spurt, and fertility. In females, estrogen produced by the ovaries triggers the development of breasts and the uterus, leading to regular menstrual cycles through the hypothalamic-pituitary-gonadal axis. In males, testicular growth is usually the first sign of puberty, occurring about six months after breast development in girls. Before the growth spurt, males gain the potential for fertility, mature body proportions, and adult testosterone levels. DSDs can impede, delay, or prevent puberty. Some DSDs can cause a cross-gender pubertal pattern characterized by the feminization of males due to excess estrogen or the virilization of females due to high androgen levels.[45]

**Classification of DSDs:-**

Different types of DSDs are classified based on variations in sex determination at various levels. These levels include genetic sex, chromosomal sex, gonadal sex, hormonal sex, ductal sex, external genitalia, secondary sexual characteristics, legally assigned sex, and psychological characteristics.[46] However, when it comes to clinical management, the classification system established by the PESLW and ESPE is followed, which includes the following categories: 1) DSD Sex Chromosomes, 2) DSD 46, XX, and 3) DSD 46, XY. It is important to note that some conditions may not fit neatly into one category and may overlap with more than one category.[1]

Table 1. Classification of DSD

| DSD sex chromosomes | DSD 46, XY | | DSD 46, XX | |
|---|---|---|---|---|
| | Disorders of testicular development | Disorders of the synthesis/ action of androgens | Disorders of ovarian development | Disorders of the synthesis/action |
| 45, X Turner syndrome and variants | complete gonadal dysgenesis | Defects in androgen synthesis | Ovo-testicular DSD | Congenital adrenal hyperplasia |

| | | | | |
|---|---|---|---|---|
| 47, XXY Klinefelter syndrome and variants | Partial gonadal dysgenesis | LH receptor defect | Testicular DSD | Aromatase deficiency |
| 45, X/ 46, XY GMD | Gonadal regression | Insensitivity androgens | Gonadal dysgenesis | Maternal luteoma |
| Ovo-testicular DSD | Ovo-testicular DSD | 5α reductase deficiency | | |
| | | Disorder AMH | | |
| | | Cloacal exstrophy | | |

Sexual determination is a complex process that involves molecular events that coordinate the development of either testes or ovaries from an undifferentiated bipotential gonad. This transformation usually occurs during fetal life, typically between weeks 6 to 7 of gestation, when two sets of internal ducts, known as Müllerian ducts and Wolffian ducts, are present.[47-48]

During the bipotential stage, various genes such as WT1, DAX1, SF-1, LHX9, LIM1, PAX2, GATA4, EMX2, and WNT4 are expressed in both XY and XX gonadal crests. These genes and gene dosage and expression levels play crucial roles in determining gonadal differentiation.[49-51] This process involves the activation of either a testis-specific or ovary-specific developmental pathway while simultaneously inhibiting the opposing pathway. During this developmental period, external genitalia display structures such as the genital tubercle, folds, and orifice. It is worth noting that a group of genes located upstream of SRY, which are not specific to any sex, play a crucial role in the early development of gonads and are essential for the overall process of sexual development. Failure or dysfunction of certain genes in this cluster can result in a condition called sex reversal.[52]

It is essential to mention that animal studies have shown evidence of pre-gonadal sexual differentiation that is not dependent on the presence or expression of the SRY gene. This phenomenon has also been observed in fertilized embryos in vitro, revealing early signs of sexual differences. Yadav et al. conducted research that showed that the first embryos undergoing one-cell division were more likely to develop into males than females. This was due to the faster cell division rate of XY mouse embryos compared to XX embryos.[53] Similar findings have been confirmed in humans[54] and are associated with the paternal X chromosome, which appears to slow down the growth of post-implantation embryos.[55]

During sexual development, certain factors can have a significant impact, as demonstrated by the role of the insulin receptor in male sexual differentiation.[56] This receptor is vital in promoting gonadal proliferation before the expression of the SRY gene. After that, two significant proteins play a crucial role in developing the bipotential gonad: the Wilms tumour suppressor (WT1) and the nuclear receptor SF-1 (also known as NR5A1). SF-1 is responsible for synthesizing adrenal and gonadal steroids and is expressed in the bipotential gonad of both sexes. Although its expression persists in the developing testes, it is suppressed in the ovary, potentially linking SRY expression with the production of antimüllerian hormone (AMH).[57] On the other hand, the WT1 gene encodes a vital transcription factor that is necessary for mesenchymal-epithelial interactions and the subsequent development of the bipotential gonad, particularly interactions between Sertoli cells and Leydig cells.[58]

Several genes play a role in gonadal differentiation, and their transcripts can be found in the urogenital ridges. Pathogenic variants in these genes hinder gonadal formation by preventing the somatic cells of the genital ridge from proliferating, even though germ-cell migration remains normal. Some of these genes, such as DMRT1, PAX2, and LHX9[59], are associated with gonadal differentiation but do not have strong testicular-promoting activity. Other genes, including SOX3, SOX9, FGF9, and PGD2,[9,60,61] have a more pronounced testicular-promoting activity. Conversely, there are genes such as DAX1, WNT4, FOXL2, RSPO1, and β-catenin that predominantly promote ovarian development[50, 62-64].

**Testicular Development**

Male sexual differentiation occurs in two stages. The first stage involves initiating testis formation from the primitive gonad, guided by various transcription factors collectively known as sex determinants. In the second stage, the internal and external male genitalia differentiate. This is orchestrated by hormones secreted by the fetal testicles, known as sex differentiation. The process includes the actions of anti-Müllerian hormone (AMH) secreted by Sertoli cells, androgens, and insulin-like factor-3 (INSL3) secreted by Leydig cells.[65]

The development of testicles is mainly determined by the SRY gene, which encodes a transcription factor that is essential for testicular development. The SRY protein produced by the gene moves toward the nucleus and binds to the enhancer region of the SOX9 gene. This binding event plays a crucial role in the proliferation differentiation of Sertoli cells and the organizational development of the testis.[66,67] Any harmful variant or loss of function in the SRY gene can cause sexual reversion from male to female or the coexistence of testicular and ovarian tissues.[68] Most pathogenic variants in the SRY gene are found within its DNA binding domain.[69]

Chromosomal translocations leading to SRY expression in XX individuals account for about 10% of female-to-male sex reversals. In contrast, in 15% of cases of gonadal dysgenesis, pathogenic variants in the SRY gene are responsible in individuals with a 46, XY karyotype.[70] Inhibition of SRY expression can also occur due to pathogenic variants in genes involved in chromatin structure, such as polycomb complexes. These genes maintain the undifferentiated state of embryonic stem cells by suppressing the expression of multiple genes. Moreover, genes such as GATA4 and its partner FOG2 also affect SRY expression. These genetic disruptions cause anatomical, physiological, and functional gonadal defects, such as complete or mixed gonadal dysgenesis.[71]

SRY is a gene that targets several other genes, such as SOX9, CBLN4, and ER71/ETV2, with SOX9 being the most important. To activate SOX9, SRY and SF-1 proteins work together on the TESCO region, which is specific to the Sox9 core.[72] Additionally, SOX9 can bind to its own promoter, which helps in controlling its own expression. Interestingly, the testicular formation can still occur without SRY, as observed in XX men with SOX9 duplications or translocations, as well as in XX transgenic mice with SOX9 overexpression.[73] Gene expression studies have shown that a decrease in SOX9 protein expression and the absence of pathogenic variants in several regions of the

gene promoter (TESCO region) were found in 75 Brazilian patients with a 46, XY karyotype and sexual reversion, suggesting alternative mechanisms of gene regulation as causative factors.[74,75] Unlike SRY, which has transient expression during gonadal development, SOX9 expression is sustained over time. [74,75]

A gene called DAX1 (also known as NR0B1) located on the X chromosome (p21.3) plays an important role in testicular gonadal development. This gene encodes a nuclear receptor, which, when duplicated in individuals with an XX karyotype, can directly inhibit SF-1, a transcription factor that regulates SOX9. This inhibition, mediated by the two functional copies of DAX1, prevents the formation of testicles[76] and has been validated in transgenic mice overexpressing DAX1 with an XY karyotype. These mice exhibited a female phenotype, confirming that gene duplication alone is sufficient to block testicular differentiation despite having the chromosomal complement.

**Ovarian Development**

Female sexual differentiation occurs when germ cells enter meiosis, a process that happens in the absence of the SRY gene.[77,78] This absence prevents the attainment of a critical threshold for SOX9 expression and promotes the expression of signalling factors like RSPO1, WNT4, and FOXL2. These factors collectively drive the formation of the ovary by differentiating precursor cells into granulosa cells while concurrently inhibiting testicular formation.[79]

In XX gonads, the signalling factors WNT4 and RSPO1 actively promote and stabilize the expression of the transcription factor CTNNB1, also known as β-catenin. CTNNB1 suppresses SOX9 expression and regulates the transcription of genes dependent on WNT4. Consequently, the presence of WNT4 interferes with the male pathway by impeding SOX9 expression.[80,81]

While SF-1 is known to play a crucial role in the initial formation of the bipotential gonad, it has also been found to be important for the maintenance of ovarian function.[82] Aberrations in genes such as SOX9, SF-1, and WT1, or duplications of DAX1 and WNT4, can result in 46XY gonadal dysgenesis.[83] Conversely, duplications of the SOX9 or SOX3 genes may lead to 46, XX testicular disorders of sex development (DSD).[84-86]

In some cases, male reversion can occur in XX individuals who lack the SRY gene due to pathogenic variants or loss of function in members of the ovarian pro-

differentiation pathway or as a result of gain-of-function pathogenic variants in genes that mimic the activity of SRY.[84]

**Epigenetics and DSD**

The study of changes in gene expression, without any modification in the DNA sequence, is known as epigenetics.[87] The primary mechanisms that control gene expression in epigenetics include DNA methylation, covalent histone modifications, and the presence of non-coding RNAs. These mechanisms are crucial during embryonic development as they help establish and maintain cell identity by modulating gene expression, a process that determines sex and differentiation.

Recent findings suggest that sexual differentiation can also be influenced by histone modifications and chromatin regulation.[88] Chromatin is responsible for the packaging of DNA, which can affect the accessibility of the transcriptional machinery and thus regulate the activity of functional and regulatory DNA sequences. Epigenetic mechanisms like covalent histone modifications, nucleosome repositioning, and chromatin remodelling are fundamental in regulating the expression of specific genes and larger genomic regions. Enzymes like histone acetyltransferases and histone deacetylases play a key role in mediating reversible histone modifications.[89] Histone modifications are crucial for gene expression regulation. Methylation of lysine 4 (H3K4me3) increases transcriptional activity, whereas methylation of lysine 9 (H3K9me) decreases it. Studies have shown that a deficiency in H3K9 demethylating enzyme in XY mice results in the development of fertile females due to the downregulation of SRY expression during embryogenesis. This suggests that histone methylation and demethylation play a vital part in mammalian sex determination.[90] Furthermore, JMJD1A, an enzyme responsible for demethylating H3K9, is important for the activation of SRY. Deficiency in JMJD1A in XY mice leads to male-to-female sexual reversion. Microarray studies, rescue experiments using transgenic mice, and chromatin immunoprecipitation confirm that JMJD1A directly catalyzes H3K9 demethylation and contributes to the activation of SRY.[91] Additionally, sexually dimorphic expression of certain ncRNAs has been identified.[92] However, the exact role of these ncRNAs in sex determination and gonadogenesis remains largely unknown and requires further study.[93]

Studies on disorders of sex development (DSD) have mainly focused on analyzing DNA methylation in patients with changes in SRY gene expression. For instance, in a

woman with primary amenorrhea and a karyotype of 46, X, inv (Y), methylation studies revealed that the CpG box located three kilobases upstream from the SRY gene had higher methylation levels in comparison to her father.[94]

**Approach to DSDs**

Individuals presenting with Disorders of Sex Development (DSD) or atypical genitalia require a comprehensive clinical assessment to establish an accurate diagnosis. This evaluation includes monitoring vital signs, a detailed physical examination, documentation of sexual characteristics, and a meticulous evaluation of the perineal region according to Prader's classification.[95] In addition, a thorough clinical history that covers prenatal and familial contexts is also taken. A collaborative team consisting of specialists such as endocrinologists, urologists, geneticists, gynaecologists, paediatricians, and psychologists work together to conduct this evaluation and provide an accurate diagnosis.[96]

In situations where assigning sex is difficult or cytogenetic tests produce inconclusive results, a thorough evaluation is necessary. Biochemical tests play a crucial role in guiding the diagnostic process by assessing gonadal function. The interpretation of these measurements considers the test characteristics and reference values specific to gestational and chronological age. In some cases, it may be necessary to perform additional measurements or stimulation tests.[97]

To diagnose a particular condition, various tests are conducted. Primary diagnostic tests include measuring 17-hydroxyprogesterone, assessing blood electrolyte levels, determining anti-Müllerian hormone (AMH) levels, measuring gonadotropin levels, conducting a cytogenetic study (karyotype), and performing an abdominal ultrasound to identify Müllerian structures. Once the results of the initial assessments are obtained, further diagnostic tests are conducted based on the findings to guide diagnostic suspicion.[98,99]

Evaluation of the disorders of sex development (DSD) is done through a genetic algorithm that considers the results of the sexual chromosomal complement.[100] FISH analysis is used to examine regions of the Y chromosome, with particular attention to the percentage of XX individuals with SRY translocation. Further evaluation involves analyzing certain genes that are essential for gonadal development (e.g. AR, SRY, SF-1, WT1, CYP21, SOX9, DAX-1, 5α-reductase, among others) using traditional molecular

research methods like Sanger sequencing along with multiplex ligand-dependent probe amplification.[101] These techniques help identify genetic abnormalities, such as gene sequence or dosage abnormalities, including gene deletions or duplications.[102-103] It is important to note that though this genetic approach has shown promise, it has so far provided an etiological diagnosis in only a limited number of cases.[66,104] For example, Laino et al.[105] reported an etiological diagnosis in only 64% of cases in an 88-individual cohort with DSD 46, XY, and 46, XX using this diagnostic algorithm.

Identifying the genes responsible for disorders of sex development (DSD) is a complex task, with several limitations associated with existing approaches. These limitations arise from the fact that many genes responsible for DSD are yet to be identified, and the methods used to study them remain inadequate. It's important to note that while pathogenic variants are a common cause of gene dysfunction, other factors, such as epigenetic modifications and transcriptional regulation, can also significantly impact gene expression. These mechanisms, including DNA methylation, covalent histone modification, and non-coding RNAs (ncRNAs), can act as biological switches.[87] Therefore, new diagnostic approaches are necessary to assess the effects of epigenetic modifications and transcriptional factors on the expression of genes crucial for sexual determination. Such approaches may lead to better detection of etiological factors in individuals with DSD.

It is crucial to remember that epigenetic changes are specific to the context and time. In people with DSD, it is essential to perform these analyses on gonadal tissue, along with a histological examination. This step is particularly crucial since people with gonadal dysgenesis have a higher risk of developing tumours, and tumours themselves may have epigenetic modifications that make it difficult to determine the real cause.

Various types of analyses can be done on gonadal tissue to study messenger RNA expression, chromatin tags, and DNA methylation status. These analyses can be conducted using techniques such as quantitative polymerase chain reaction, RNA sequencing, chromatin immunoprecipitation, bisulfite modification-sequencing, or methylation-specific polymerase chain reaction. The aim of these approaches is to gain a better understanding of the networks that regulate gonadal gene expression and how they contribute to the development of specific DSD phenotypes.[66,106]

Helder A. conducted a study that involved a comprehensive clinical evaluation and minimal investigations, including chromosomal, hormonal, biochemical, radiological, gonioscopy, and laparoscopy/laparotomy/gonadal biopsy.[25] The cases were categorized into three main groups: 46, XY disorder of sex development (40 cases/63.5%), 46, XX disorder of sex development (14 cases/22.2%), and gonadal differentiation disorder of sex development, which included Ovo-testicular disorder of sex development and gonadal dysgenesis (9 cases/14.3%).In the group of 46, XX disorder of sex development, the primary presentations were ambiguous genitalia and precocious puberty. Conversely, in the 46, XY disorder of sex development group, the main presentations were ambiguous genitalia and underdeveloped or pubertal breast development. Ambiguous genitalia were the primary presenting complaint in cases of gonadal differentiation disorder of sex development. The age at presentation exhibited three peaks: infancy, childhood, and the post-pubertal period. Additionally, remnants of Müllerian ducts were identified in nine (22.5%) cases within the 46 XY disorder of sex development group. Male-like external genitalia with bilateral cryptorchidism were evident in cases of 46, XX disorder of sex development. The process of sex assignment or reassignment was primarily based on the degree of virilization of the external genitalia, specifically phallus size, and the response to testosterone, with the exception of cases in the 46, XX disorder of sex development group.

In conclusion, Helder A.'s study demonstrates that meticulous clinical evaluation coupled with baseline investigations is instrumental in effectively managing cases of disorder of sex development.[25]

In a study conducted by Shamma RA et al., it was found that among 100 patients, 71% had been diagnosed with 46XY Disorders of Sex Development (DSD), 24% with 46XX DSD, and 5% with sex chromosome DSD. The median age at which DSD symptoms appeared was 12 months, and 19% of the cases were identified during infancy. The main cause of 46XY DSD was either defects in androgen synthesis or action, accounting for 40% of cases, with the majority being attributed to androgen insensitivity syndrome (28%). In the case of 46XX DSD patients, the majority (21 out of 24) received a diagnosis of classic CAH secondary to a deficiency in the 21-hydroxylase enzyme, with 90% of these cases manifesting as salt-wasting CAH. The study concluded that 46XY DSD was the most prevalent etiological diagnosis in cases of DSD, with androgen insensitivity syndrome being the most common causative factor. Classic salt-wasting

CAH emerged as the second most frequent disorder. Managing children with DSD is challenging, especially in settings with limited resources. The primary obstacles to achieving accurate diagnosis and effective management include delayed presentation, economic constraints, and socio-cultural factors.[107]

A study conducted by R. Walia et al. revealed that out of the total number of patients, 52.5% were diagnosed with 46, XY DSD, 38.1% were identified as 46, XX DSD, and 3.6% were found to have sex chromosome DSD. Among the patients with 46 XY DSD, 31.4% had androgen insensitivity syndrome, and 25.5% were attributed to androgen biosynthetic defects. The majority (70.27%) of patients with 46, XX DSD were diagnosed with congenital adrenal hyperplasia (CAH), while 10.8% had ovo-testicular DSD. Among the patients with sex chromosome DSD, five exhibited mixed gonadal dysgenesis. The study concludes that congenital adrenal hyperplasia is the most prevalent DSD. The most common XY DSD diagnosis is androgen insensitivity syndrome, while CAH is the predominant XX DSD diagnosis. The study highlights the issue of delayed diagnosis and corrective surgeries being performed without a definitive diagnosis being established beforehand.[24]

According to a study led by Ganie Y, 416 children (15.1%; CI: 13.8%–16.5%) in sub-Saharan Africa were diagnosed with Disorders of Sex Development (DSD). The most common diagnosis was 46 XY DSD related to androgen synthesis and action, followed by ovo-testicular DSD. Congenital adrenal hyperplasia (CAH) was the third most common disorder. The study also found that 97% of African patients who received a diagnosis had 46 XX DSD, and prematurity was present in 47% of children with DSD ($p<0.001$).[108]

The aetiological diagnosis revealed that sex chromosome DSD accounted for 9.5% (n=33) of the cases, 46 XX DSD for 33% (n=114), and 46 XY DSD for 57.5% (n=199) [105]. Among these, the most prevalent diagnoses, in descending order, were disorders in androgen synthesis and action (not classified), accounting for 53% (n=182) of cases, followed by ovo-testicular DSD at 22% (n=75), and congenital adrenal hyperplasia (CAH) at 10% (n=36). The median age at presentation across all cases was ten months (IQR: 1 month–4.5 years), and a significant correlation ($p<0.001$) between the age of presentation and the aetiological diagnosis was seen.[108]

The study conducted by Misgar RA et al. analyzed 73 cases of Disorders of Sex Development (DSD) and revealed that DSD is not an uncommon diagnosis among African patients in sub-Saharan Africa [106]. The study emphasizes the importance of early diagnosis and management of DSD, especially since prematurity was found to be a significant risk factor. Among the 73 cases analyzed, 29 patients (39.7%) were diagnosed with 46 XY DSD, 29 patients (39.7%) were identified as having 46 XX DSD, and 15 patients (20.5%) had sex chromosome DSD. Within the 29 patients diagnosed with 46 XY DSD, 17 individuals (58.6%) were diagnosed with 5α-reductase type-2 deficiency (5α-RD), and six patients (20.7%) presented with complete androgen insensitivity syndrome. Notably, a history of consanguinity was documented in nine (52.9%) patients with 5α-RD. Additionally, two patients exhibited testosterone biosynthetic defects, and one patient had partial androgen insensitivity syndrome. Among the 29 patients with 46 XX DSD, 16 patients (55.1%) were diagnosed with congenital adrenal hyperplasia (CAH). Of the 15 patients with sex chromosome DSD, seven were identified with Turner's syndrome, seven with Klinefelter's syndrome, and one with mixed gonadal dysgenesis.[109]

Overall, the study revealed that an equal number of patients were diagnosed with 46 XY DSD and 46 XX DSD. The common cause of 46 XY DSD in India is 5α-RD, while CAH remains the predominant cause of 46 XX DSD, as previously documented in the literature.

# AIMS AND OBJECTIVES

**Primary: -** To Study the relative incidence of various types of DSDs presenting to AIIMS Bhopal and its comparison with data from other regions

**Secondary:**-

1. To study the total incidence of DSDs in the patients being investigated as per existing protocols (positivity rate)
2. To study the occurrence of various morphological features in a particular type of DSDs

# MATERIAL AND METHODS

**Study Design:**

The present study is a Hospital-based Clinico-epidemiological observational study in the Department of Pediatric Surgery at the All-India Institute of Medical Sciences, Bhopal. This cohort consisted of data from Feb 2022 to Aug 2023, spanning one and a half years.

**Ethical Consideration:**

This study was conducted in compliance with the guidelines outlined in the International Conference on Harmonization Good Clinical Practice (ICH-GCP), considering all requisite precautions. Ethical approval was obtained from the Ethics Committee of AIIMS Bhopal. Prior to participation in the study, written consent was obtained from each participant, parent, or caregiver in their native language.

**Autonomy:**

- Anonymity: All documents related to procedures and records of interactions/interviews were anonymised.
- Informed Consent: Participants were provided with a comprehensive Patient Information Sheet outlining potential risks and benefits and given ample time for consideration.
- Confidentiality: All data was stored in a highly confidential manner.

**Beneficence and non-malfeasance**:

- The present study aimed to enhance the standards of care for participants, with no intention to exploit or harm any individual. As healthcare professionals, the well-being of participants was the top priority. Participants were informed about care, potential risks, and benefits through a written Participant Information Sheet.
- Visits or interviews were semi-structured to ensure the comfort of patients and provide them with the opportunity to express their views, concerns, and doubts to the research team, with these interactions explained in the participant information sheet.
- Researchers conducted participant interviews during their own time to minimize any impact on clinic schedules.

**Patient Sampling and Methodology**:

Patients aged one day to 18 years visiting the AIIMS hospital facility in Bhopal were included in the study if they exhibited the following conditions:

- Hypospadias with un-descended testis
- Hypospadias with bifid scrotum
- Micro penis
- Bilateral Female inguinal hernia
- Bilateral un-descended testis
- Clitoromegaly
- Patients referred to our institute for further management of DSD (Disorders of Sex Development)
- Incidentally found DSD in patients with other complaints

**Exclusion criteria**:

- Age exceeding 18 years
- Hypospadias without un-descended testis or bifid scrotum

Detailed patient history, including a three-generation pedigree, age of presentation, gender of rearing, consanguinity, family history of similar disorders, pregnancy details, antenatal exposure to androgens/estrogens, recurrent infections/diarrhea/hospitalisation, and previous neonatal deaths, will be documented. Comprehensive clinical examinations, encompassing hyperpigmentation (particularly in genital skin and nipples), hypertension, hydration status, associated anomalies, and secondary sexual characteristics in peripubertal patients, will be recorded. Genital ambiguity, including phallic length, palpable gonads and their location, urethral opening position, presence of a common urogenital sinus, labio-scrotal folds, degree of fusion, rugosity, and pigmentation, will also be documented.

Clitoromegaly (or macroclitoris) is an abnormal enlargement of the clitoris. Clitoromegaly will be considered when the crosswise width of the glans is >5 mm between 0–3 years, >6 mm between 4–8 years, >5 mm between 9–12 years, and >8 mm between 13–16 years; when its lengthwise width is >5–6 mm; and when the length of the hood is >12.6 mm between 0–3 years, >18.8 mm between 4–8 years, >24.2 mm between 9–12 years, and >27.4 mm between 13–16 years.[110]

A correct and accurately measured penile length of -2.5 SD below the mean for age and presence of internal and external genital organs compatible with a 46, XY karyotype are sufficient findings to support a diagnosis of micropenis.[111] To label micropenis the penile length corresponding to the -2.5 SD value for 0-5 months will be taken as <1.9 cm, at 6-12 months as <2.3 cm, at 1-2 years as < 2.6 cm, at 2-3 years as <2.9 cm, at 3-4 years as <3.3 cm, at 4-5 years as <3.5 cm, at 5-6 years as <3.8 cm, at 6-7 years as <3.9 cm, at 7-8 years as <3.7 cm, at 8-9 years as <3.8 cm, at 9-10 years as <3.8 cm, at 10-11 years <3.7 cm and for 12 years or more as <9.3 cm.[112]

Bifid scrotum consider if there is separation of both scrotum is >30 % of total scrotal length or >1/3 of midline of scrotum.

Congenital penile torsion is a malformation of unknown cause in which there is a three-dimensional malrotation of the corporal bodies or sometimes just the glans.

Torsion of the penis can vary in severity ranging from 30 degrees in mild cases to 180 degrees, and actual degree of the torsion including the direction (clock-wise/ anti clock-ise) will be recorded.

The investigation protocol and management will be recorded in accordance with the respective consultant's recommendations. For the retrospective cohort, patient details from the specified period were retrieved from hospital records and follow-up visits.

All individuals with 46XY Differences of Sex Development (DSD) were subjected to a human chorionic gonadotropin (hCG) stimulation test, excluding those with complete androgen insensitivity syndrome (CAIS). The test involved administering intramuscular injections of 1000–1500 units of hCG for three consecutive days, with serum testosterone (T) levels measured before the first injection and 24 hours after the third injection. A response indicating a twofold or greater increase in T level was deemed indicative of functional testes. Additionally, a testosterone to dihydrotestosterone (DHT) ratio exceeding 20 was suggestive of 5α-reductase type-2 deficiency (5α-RD).[111]

The diagnosis of an androgen biosynthetic defect, specifically 17β-hydroxysteroid dehydrogenase type-3 (17β-HSD3) deficiency, was based on low T levels and elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) values, along with a T/A ratio of less than 0.8 in response to hCG stimulation during both pubertal and post-pubertal stages.[112] For all patients with a 46, XX karyotype, the evaluation encompassed the estimation of 8 AM or random serum cortisol, 17-hydroxyprogesterone (17-OHP), testosterone, LH, and FSH. The diagnosis of congenital adrenal hyperplasia (CAH) will

be considered when unstimulated and/or stimulated (following intravenous injection of 250 μg of Tetracosactin) 17-OHP levels exceeds 10,000 ng/dl.[113]

**Data Collection and Analysis: -**

Data will be collected and organized using Microsoft Excel **Microsoft® Excel® 2021 MSO (Version 2309 Build 16.0.16827.20166) 64-bit.** The results of the present study were compared to all available national and international studies.

# RESULTS

In this observational study, we enrolled 40 patients according to the inclusion criteria, during the period of study Feb 2022 to Aug 2023.

The general demographic characteristics of the participants, including their age distribution, and mean age, are presented in Table 2. The mean age of the study participants was 5.38 ± 3.91 years. The highest incidence was observed in the age group of 1 to 5 years, with 20 cases, followed by the age groups of 5 to 10 years (10 cases), 10 to 15 years (5 cases), and 1 day to 1 year (5 cases), as shown in both Table 2 and Figure 1. Gender distribution of study participants showed male dominancy with 31 males and 09 females with around a 3.44:1 M: F ratio.

**Table no. 2- Age and sex-wise (rearing)distribution**

| | Male (n=31) | Female (n=9) | Total |
|---|---|---|---|
| 0 days – 12 months | 3 | 2 | 5 |
| One year – 5 years | 16 | 4 | 20 |
| Six years – 12 years | 9 | 3 | 12 |
| 13 years – 18 years | 3 | 0 | 3 |
| Mean age - 5.38 ± 3.91 years | | | |

**Figure no.1-Age & Sex wise (rearing) distribution**

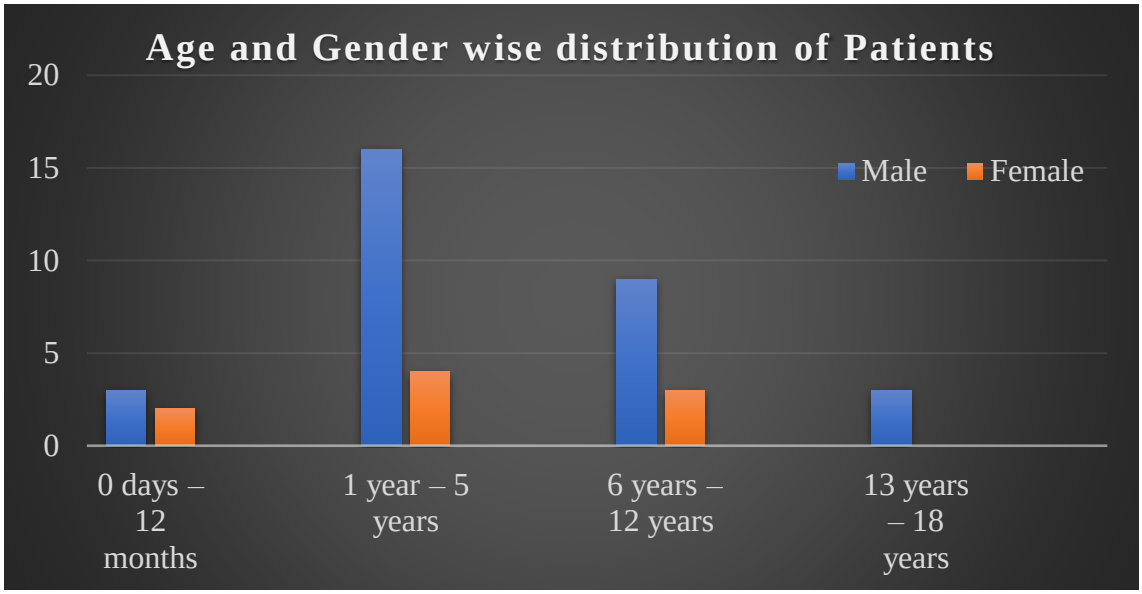



**Table no. 3– Distribution according to gender of rearing**

| Sex of rearing | Number | Gender assigned (Karyotyping) Male | Gender assigned (Karyotyping) Female | Total |
|---|---|---|---|---|
| Male | 31 | 29 | 2 | 31 |
| Female | 09 | 0 | 9 | 09 |

**Figure no.2 Distribution according to gender of rearing**

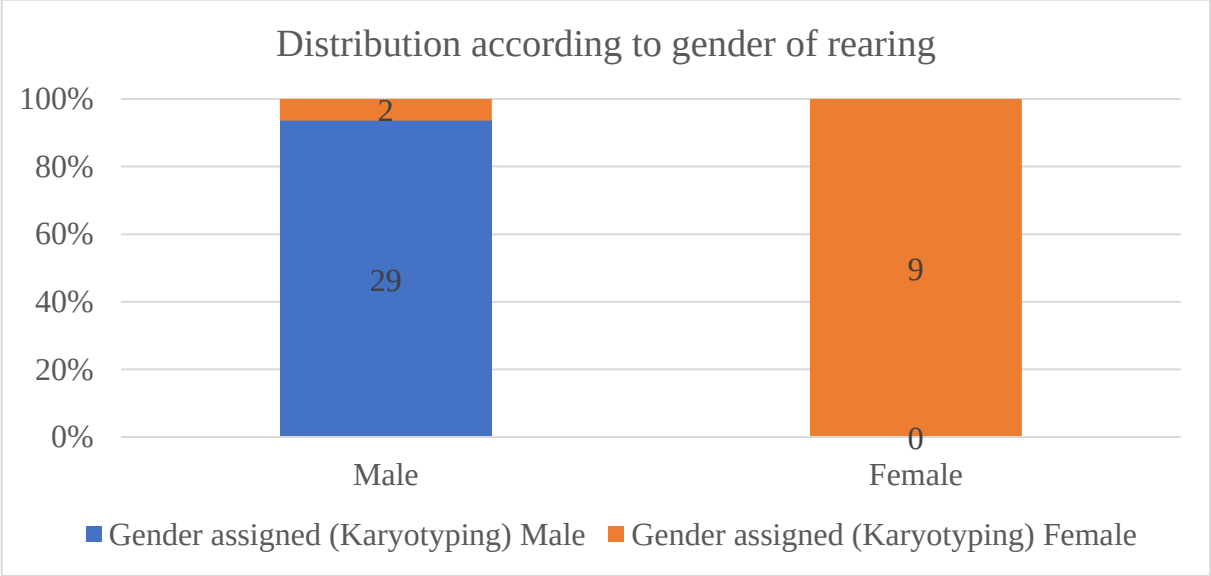


**Table no. 4- Distribution of patients according to Presenting complaint**

Table 4 provides an overview of the primary reasons for hospital visits, with the most prevalent chief complaint being the passage of urine from beneath the penile surface, accounting for 13 cases. This was followed by the passing of urine undersurface of the penis with an empty scrotum in 7 cases, followed by female inguinal hernia, isolated bilateral empty scrotum, Micropenis, and clitoromegaly.

| Symptoms (parameter) | Male (Number) | | Female |
|---|---|---|---|
| The passing of urine under the surface of the penis and empty scrotum | 07 | | NA |
| passing of urine under the surface of the penis | 13 | | NA |
| Undescended Testis | Unilateral | Bilateral (03) | 00 |
| Microphallus | 03 | | 00 |
| reducible swelling in the inguinal region | Unilateral 00 | Bilateral 01 | B/L (03)<br>U/L (04) |
| Large Clitoris | NA | | 02 |

**Table no.5-Diagnosis of patients according to phenotypes**

| S.N. | Phenotype | No of patients | Positivity rate |
|---|---|---|---|
| 1 | Proximal hypospadias | 17 | 07 |
| 2 | Hypospadias with undescended testes | 09 | 05 |
| 3 | Bilateral inguinal female hernia | 7 | 0 |
| 4 | Bilateral undescended testes | 2 | 0 |
| 5 | Micropenis | 2 | 1 |
| 6 | Micropenis with UDT | 1 | 1 |
| 7 | Clitoromegaly | 2 | 1 |

In the current investigation, a 35% incidence rate of Disorders of Sex Development (DSD) was observed. Specifically, 14 patients were identified as having DSD, and their distribution is delineated in Table 5 and Figure 3. Of the 11 cases of proximal hypospadias, 4 were determined to have DSD. In the subgroup of 11 cases with hypospadias and undescended testes, 7 were diagnosed with DSD. Within the cohort of 3

micropenis cases, 2 case was ascertained to have DSD, and out of the 2 cases of clitoromegaly, 1 case was also identified as having DSD.

**Figure no.3-Diagnosis of patients according to phenotypes**

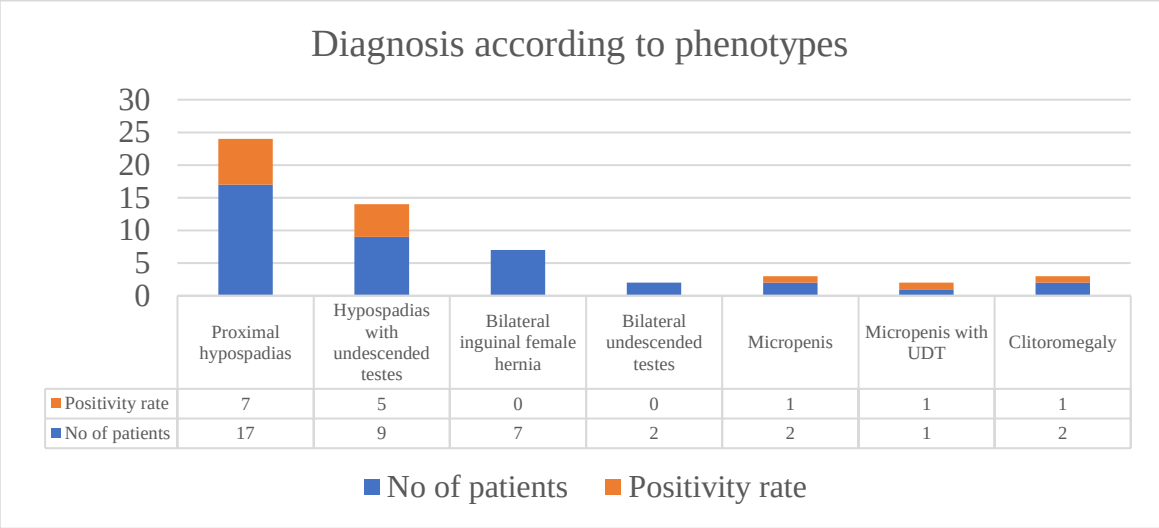



Table 6 describes the characteristics of genitals and gonads in males. 01 had an absent dorsal hood, in meatal opening 8 had a penile shaft opening, 11 had penoscrotal, 04 had scrotal, and 2 had a perianal opening. 06 had a flat glance while 24 had a conical glance.01 had a fused scrotum, 15 had a bifid scrotum, and 06 had an undeveloped scrotum.

**Table no. 6-Characteristics of Genitals & Gonads in male**

| Character | Types | Number |
|---|---|---|
| **dorsal hood** | Present | 29 |
| | Absent | 01 |
| **meatal opening** | Glans | 06 |
| | Penile shaft | 08 |
| | Penoscrotal | 11 |
| | Scrotal | 04 |
| | Perineal | 02 |
| **Chordee** | >45 | 20 |
| | <45 | 06 |
| | No chordee | 03 |
| | Operated | 01 |

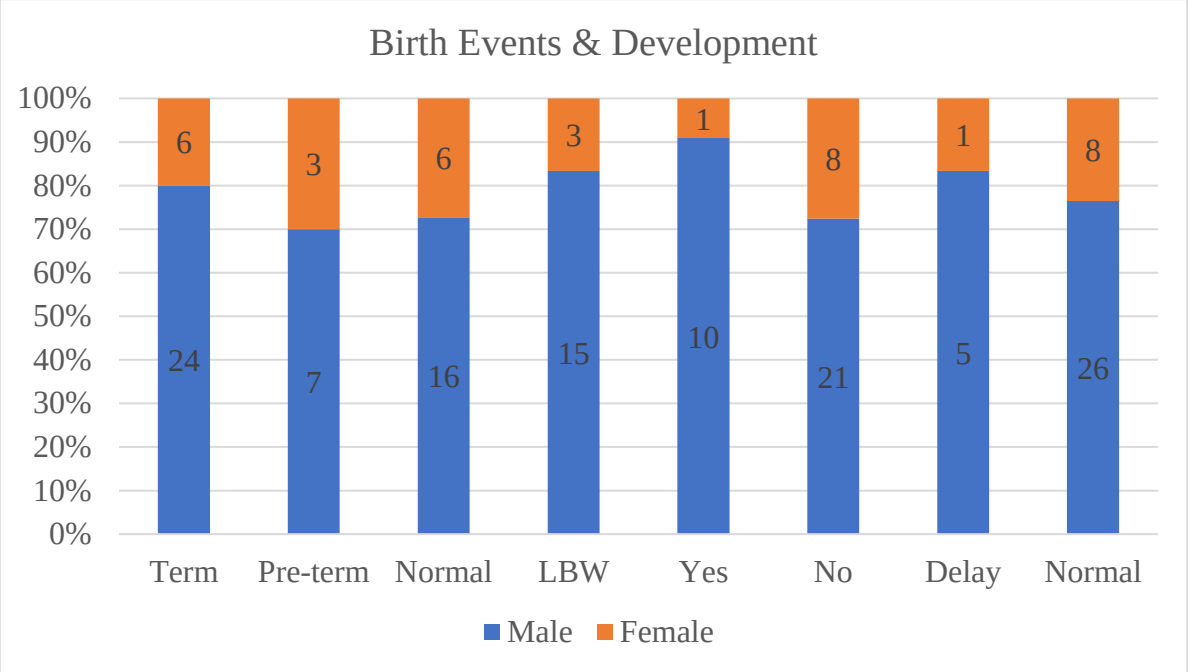
| | | | |
|---|---|---|---|
| **SPL** | <2.5 | | 07 |
| | 2.5 | | 08 |
| | >2.5 | | 15 |
| **Glans** | Flat | | 06 |
| | Conical | | 24 |
| **Scrotum** | Fused, penoscrotal web | | 01 |
| | Bifid | | 15 |
| | Underdeveloped | | 06 |
| **Position of Gonads** | Non-palpable | | 06 |
| | Palpable | Scrotum | 17 |
| | | Inguinal | 09 |
| | | Other sites | 00 |

**Table no. 7-Distribution according to Birth Events & Development**

| Gender | Gestation age | | Birth weight | | NICU Stay | | Development | |
|---|---|---|---|---|---|---|---|---|
| | Term | Pre-term | Normal | LBW | Yes | No | Delay | Normal |
| Male | 24 | 7 | 16 | 15 | 10 | 21 | 5 | 26 |
| Female | 6 | 3 | 6 | 3 | 1 | 8 | 1 | 8 |

Among a sample of 31 males, 24 exhibited term gestational age, while 7 presented with preterm gestational age. Among a group of 9 females, 6 were born at term gestational age, while 3 were born preterm. In terms of birth weight, 16 males and 6 females demonstrated normal birth weight, while 15 males and 3 females had low birth weight. Regarding Neonatal Intensive Care Unit (NICU) stay, 10 males and 1 female required NICU care following delivery. Out of the total 40 patients, 5 males and 1 female experienced developmental delay (Table 7, Fig.4).

**Figure no 4-Distribution according to Birth Events & Development**

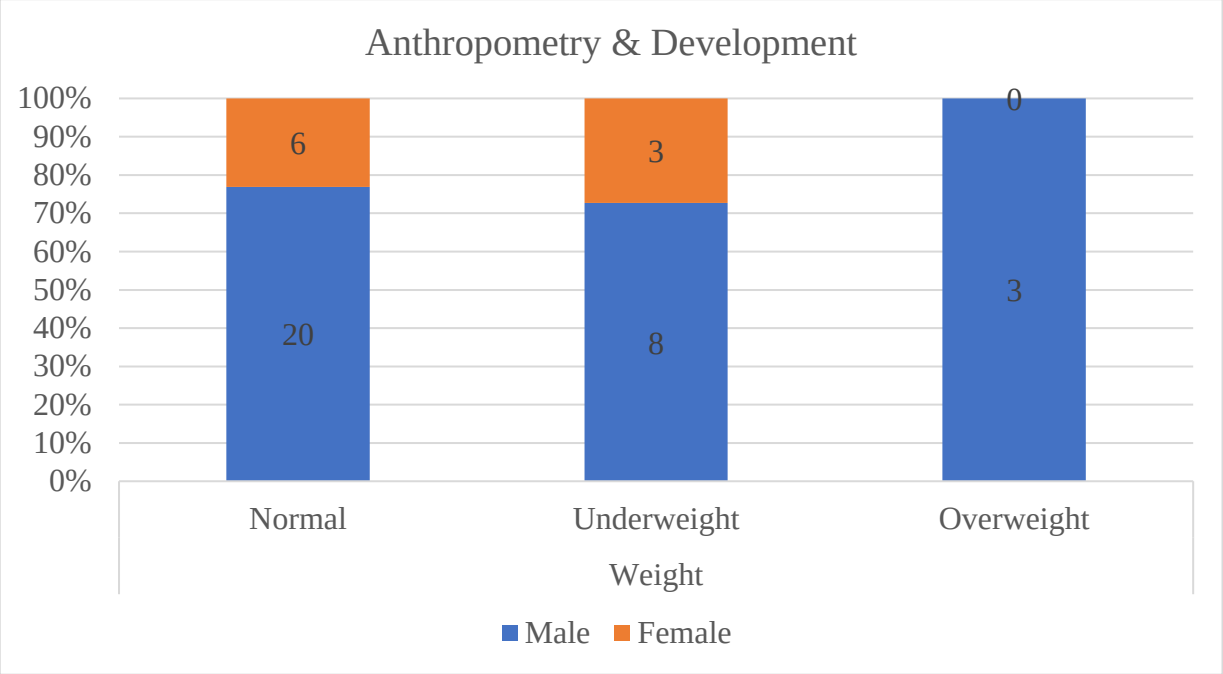



In a cohort of 31 males, 20 exhibited normal weight, 8 were underweight, and 3 were overweight, as indicated in Table 5 and Figure 5. Among the 9 females included in the study, 6 demonstrated normal weight, 3 were underweight, and none fell into the overweight category (Table 8, Figure 5).

**Table no 8-Distribution of patients according to Anthropometry & Development**

| Gender | Weight | | |
|---|---|---|---|
| | Normal | Underweight | Overweight |
| Male | 20 | 8 | 3 |
| Female | 6 | 3 | 0 |

**Figure no 5.-Distribution of patients according to Anthropometry & Development**




The blood pressure of the study participants was described in Table 9, Fig.6. Only one male had hypertension.

**Table no. 9- Distribution of patients with blood pressure**

| Gender | Normal | Elevated | Hypertension |
|---|---|---|---|
| Male | 23 | 07 | 01 |
| Female | 09 | 00 | 00 |

**Figure no 6-Distribution of patients with blood pressure**

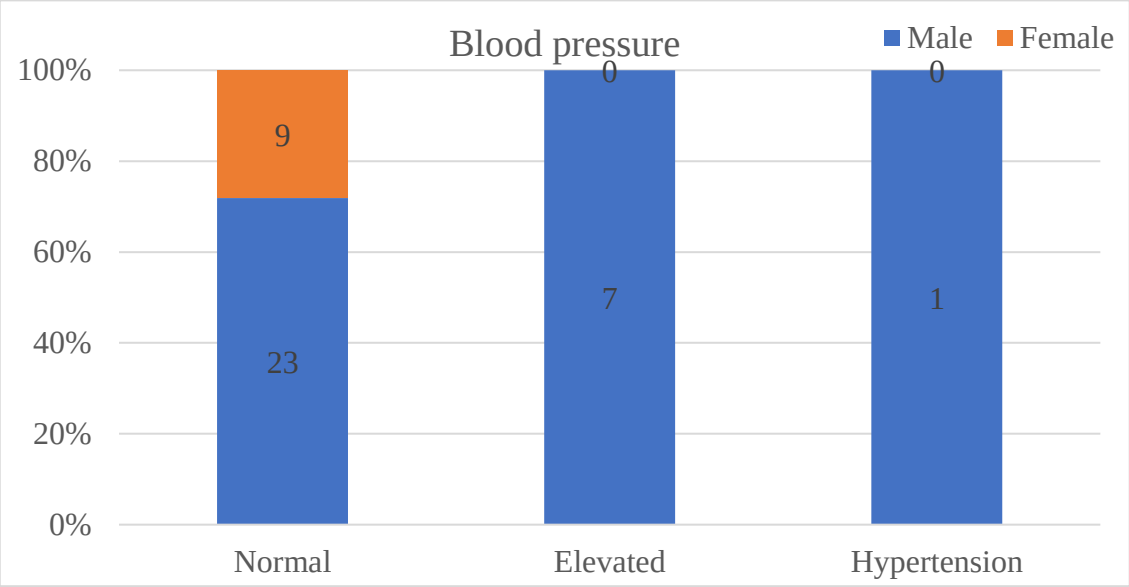


**Table no.10- Distribution according to karyotyping**

| According to karyotyping | | |
|---|---|---|
| S.N. | Karyotyping | No of patients |
| 1 | XY | 27 |
| 2 | XX | 11 |
| 3 | XX with SRY translocation | 1 |
| 4 | XY +m chromosome | 1 |

Based on karyotyping analysis, the prevailing occurrence was the presence of XY in 27 patients, succeeded by XX in 11 patients. In addition, one patient exhibited an XX karyotype with SRY translocation, and another patient had an XY karyotype with an additional m chromosome (Table 10, Figure 7).

**Figure no .7- Distribution according to karyotyping**

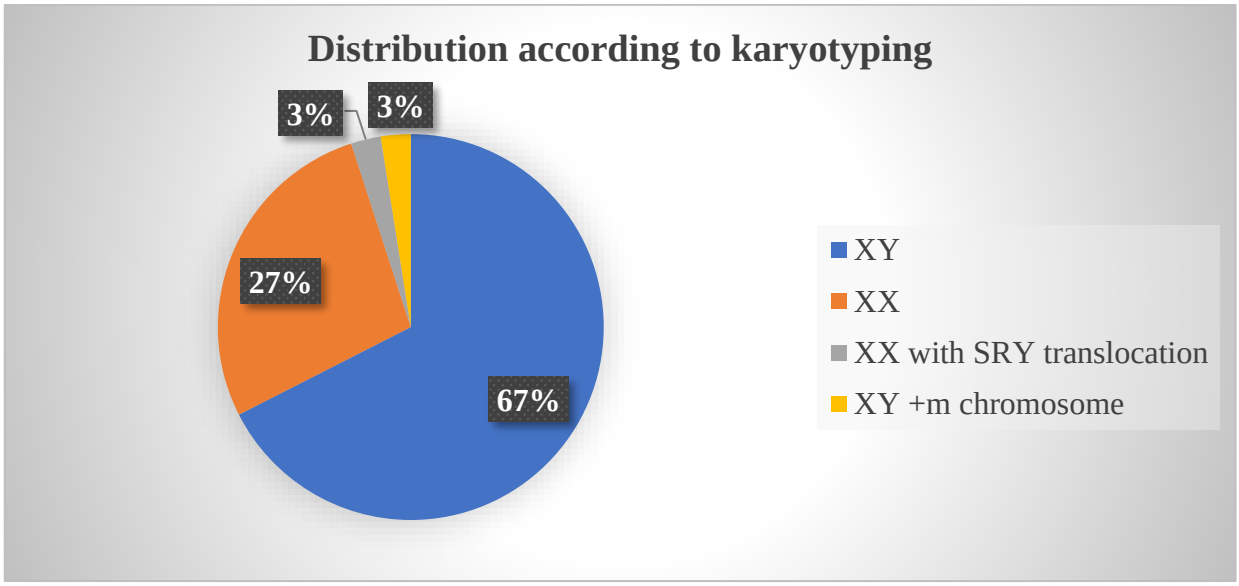



**Table no. 11 - Diagnostic criteria for DSD - CAH**

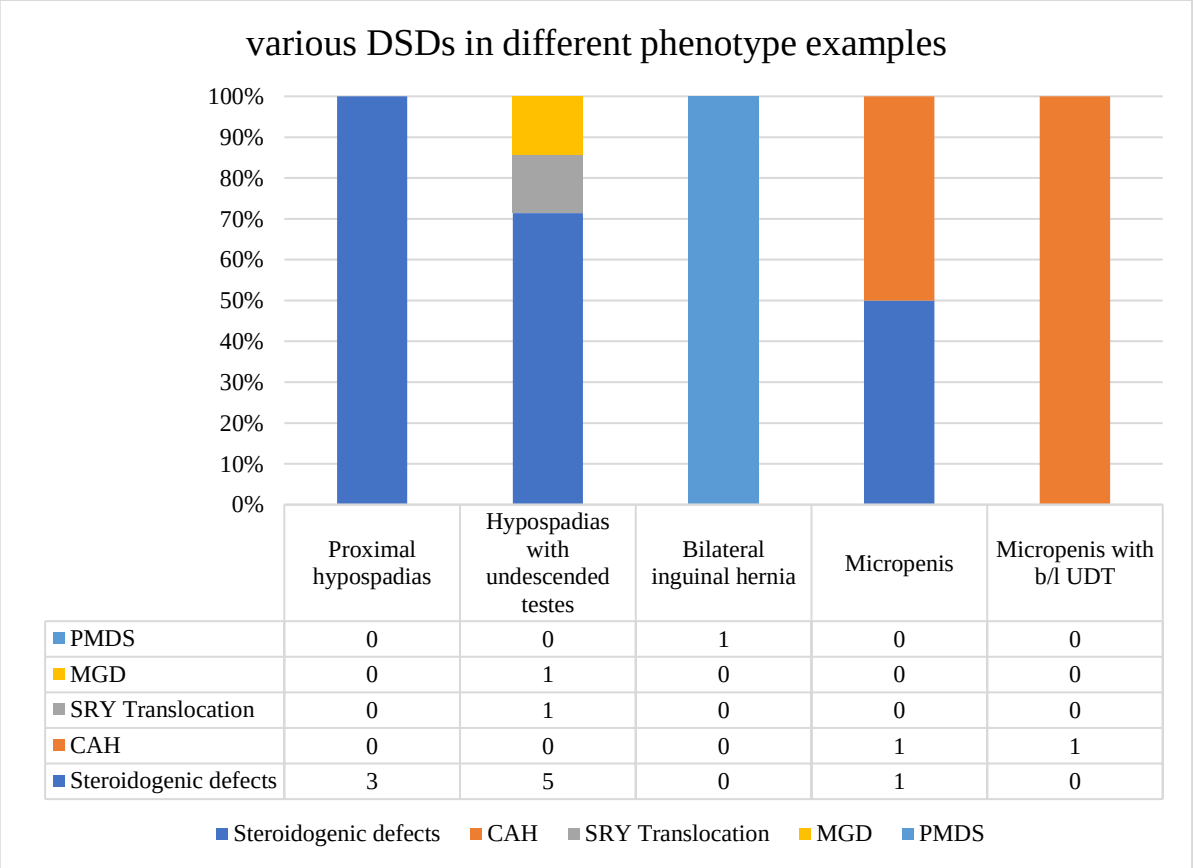
| | **Clinical Presentation** | **Karyotyping** | **Na** | **K** | **17 OHP** |
|---|---|---|---|---|---|
| Child 1 | Clitoromegaly | 46, XX | 107 | 3.68 | >200 ng/ml |
| Child 2 | Micropenis with b/l UDT | 46, XX | 137 | 4.27 | >20ng/ml |

**Table no 12- Multiple tables depicting various DSDs in different phenotype**

| | Proximal hypospadias | Hypospadias with undescended testes | Bilateral inguinal hernia | Micropenis | Micropenis with b/l UDT |
|---|---|---|---|---|---|
| Steroidogenic defects | 03 | 5 | 0 | 1 | 0 |
| CAH | 0 | 0 | 0 | 1 | 1 |
| SRY Translocation | 0 | 1 | 0 | 0 | 0 |
| MGD | 0 | 1 | 0 | 0 | 0 |
| PMDS | 0 | 0 | 1 | 0 | 0 |

Table 12 provides an overview of the phenotypes observed in various Disorders of Sex Development (DSD). In this study, the most prevalent cause of DSD was found to be steroidogenic effects, affecting 9 patients. This was followed by 2 patients with Congenital Adrenal Hyperplasia (CAH), as well as cases involving SRY translocation, Mixed Gonadal Dysgenesis (MGD), and Persistent Müllerian Duct Syndrome (PMDS).

**Figure 8. Multiple tables depicting various DSDs in different phenotype examples**




| | Proximal hypospadias | Hypospadias with undescended testes | Bilateral inguinal hernia | Micropenis | Micropenis with b/l UDT |
|---|---|---|---|---|---|
| PMDS | 0 | 0 | 1 | 0 | 0 |
| MGD | 0 | 1 | 0 | 0 | 0 |
| SRY Translocation | 0 | 1 | 0 | 0 | 0 |
| CAH | 0 | 0 | 0 | 1 | 1 |
| Steroidogenic defects | 3 | 5 | 0 | 1 | 0 |

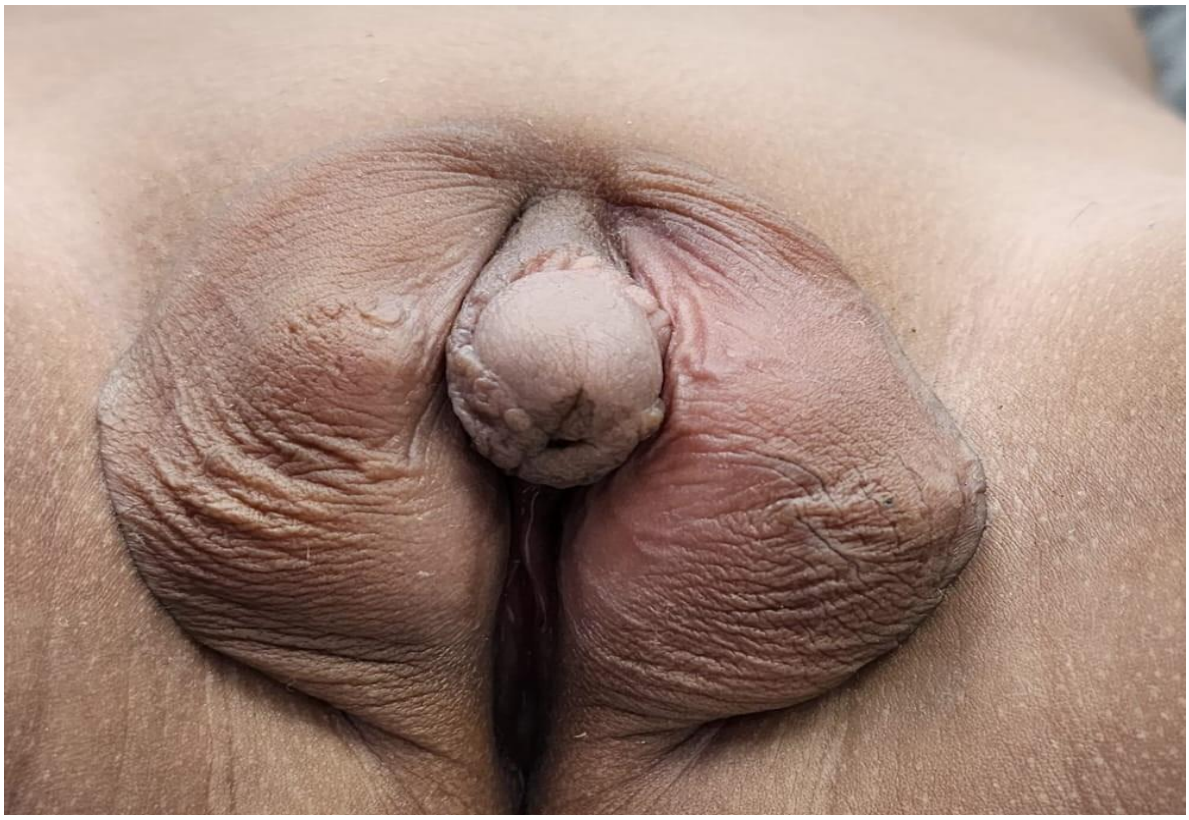


**Figure No. 9-Bifid scrotum with proximal penile hypospadias**

**Figure no 10- Micropenis**

# DISCUSSION

Disorders of sex development (DSD) represent intricate conditions arising from deviations in sex determination and differentiation processes. DSD is characterised by incongruence between genetic, gonadal, and genital sex, affecting approximately 1 in 4,500 individuals in the general population. It constitutes a complex and frequently diagnosed set of conditions, exerting a lifelong impact on affected individuals and their families. The presentation of genital ambiguity in DSD varies depending on the underlying aetiology, underscoring the importance of precise and early diagnosis for appropriate classification, treatment, and management of this condition.

DSD can be categorised into three principal groups based on the nature of abnormalities observed in sex chromosomes, testicular differentiation (XY DSD) and ovarian determination (XX DSD). This study aimed to investigate the clinical manifestations, types, frequencies, and associated genetic defects in individuals with disorders of sex development. The study encompassed a cohort of 14 index patients out of 40 individuals screened, all of whom were registered at the Department of Pediatric Surgery AIIMS, Bhopal. Data collected included information on the age at presentation, primary complaints, gender assigned at birth, and any associated abnormalities. Additionally, a three-generation pedigree analysis was performed, encompassing details such as a history of consanguinity, genital ambiguity, and infertility.

The prevalence of abnormal karyotypes in our cohort of patients with Disorders of Sex Development (DSD) was 14.28%, consistent with the results reported in a study conducted in South Africa involving 2,753 patients.[108] In that particular study, approximately 15.1% of the patients (n=416) received a diagnosis of DSD.[108] Al-Alawi et al. and Geckinli et al. have reported higher rates of chromosomal abnormalities in Omani (24.2%) and Turkish (25%) populations, respectively.[114,115] Concurrently, comparable Indian studies by Jyothy et al. (2002) indicated a similar incidence of chromosomal abnormalities (20.95%) in the southern region,[116] while Anupam et al. (2004) reported a slightly higher rate (25.6%) in the northern Indian population.[117] Discrepancies across these studies may be attributed to variations in sample sizes, selection criteria, and differences in the classification of abnormalities based on karyotyping. Our findings align with most studies in the literature, both nationally and internationally.

The patients in our study were categorised in accordance with the currently recommended classification by the LWPES and ESPE. XY DSD (n=10; 74.42%) emerged as the most prevalent abnormality in this investigation, followed by XX DSD (n=3; 21.42%) and sex chromosome DSD (n=1; 7.14%). Similar results were observed in a comparable Indian study conducted by Walia et al.,[24] where 46, XY DSD constituted the majority (52.5%), followed by XX DSD (38.1%), and sex chromosome DSD at a notably lower rate (3.6%). Conversely, in a related Indian study, both XX DSD and XY DSD had an equal prevalence (47.4%).[118] In a study by Ganie et al. (2016), XY DSD was the most common disorder, followed by XX DSD in 57.5% and 33% of the patients, respectively. However, the frequency of sex chromosome DSD was consistent with our findings (10%) and those of Ganie et al. (9.5%).[108] Bhansali et al. reported a lower incidence of sex chromosome DSD (n=4; 4.2%) in their study.[118]

The observed disparities in the prevalence of various types of Disorders of Sex Development (DSD) in various studies can be ascribed to the following factors: i. Variability in the sample size of the patient population; ii. Inconsistencies in adopting or adhering to the new classification system for defining the aetiology of DSD by clinicians; iii. Inadequate elucidation of the patient's phenotype, genotype, and gonadal status through conventional and molecular genetic analysis for categorising patients, often due to limited access to advanced diagnostic methodologies; and iv. Other socioeconomic factors.

During the study period, 40 patients, ranging in age from 3 days to 15 years, were documented. The mean age at presentation was 5.38 ± 3.91 years, a finding that aligns with the study conducted by Ashutosh H et al., where the mean age was 64 months (5.33 years).[25] Among these 40 patients, nineteen (30%) presented in infancy (below one year of age), 29 (46%) presented between 1 and 10 years, and 15 (24%) presented at an age older than 10 years.[25] This contrasted with the study by Ganguly and Sahni, where the mean age was 18 ± 2.5 years (ranging from 13 to 22 years).[119] Among the 223 female subjects in the study, 43.2% fell within the 15-20 years age group, followed by 13.6% in the 20-25 years age category. Of the 27 male subjects, approximately 3.6% were between 1-5 years of age, with 2.4% being infants below one year. In both sexes, only one neonate (0.8%) was registered, presenting with ambiguous genitalia at birth.[119] These findings are consistent with those of Al-Alawi et al., where around 60% of their patients were adults,

with only 28% in the neonatal period.[114] Approximately 1% of neonates are born with some degree of genital ambiguity, but only 0.1-0.2% of them seek medical assistance.[120]

The frequency of DSD varies depending on the underlying aetiology and ethnic background. The age at which patients with DSD are referred is 6.1 ± 7.4 years. Factors such as a lack of awareness among patients, parents, and primary care providers and socioeconomic issues may contribute to delayed referrals. Only 37.5% (n=15) of patients with a mean age of 0.45 years were referred within the first year of life, which is lower than the 58% reported by Joshi et al. in a study from India.[26] In Western countries, roughly 75% of patients are identified with the disorder before age two, in contrast to the 37.5% in our study.[121]

In this investigation, Steroid synthesis defects emerged as the predominant etiological factor for 46, XY Disorders of Sex Development (DSD), while Congenital Adrenal Hyperplasia (CAH) constituted the exclusive diagnostic category among patients with 46, XX DSD. Notably, some other studies have reported a similar pattern, with Androgen Insensitivity Syndrome (AIS) being the primary etiological diagnosis for 46, XY DSD, and CAH for 46, XX DSD.[24,26]

A retrospective analysis of 93 patients with 46 XY DSD reported that 50.5% had no defined aetiology, and 20.4% were diagnosed with AIS.[122] Another study involving 102 patients with 46 XY DSD indicated that 32 (31.4%) had Androgen Insensitivity Syndrome.[24] A study with 19 patients presenting 46 XY DSD identified 1 case of CAIS, 3 cases (15.8%) of PAIS, and 4 cases (21.05%) of 5αRD.[123] In the study by Walia R. et al., 9 (4.6%) cases of 5αRD were identified, with Gonadal Dysgenesis recorded in 17 cases, including 2 (1.5%) in the 46, XY DSD category and 14 (7.2%) in the 46, XX DSD category.[24] Within the realm of 46, XX DSD, our study noted two patients diagnosed with CAH, with one patient (50%) categorised as a simple virilising type and the other (50%) as a salt-wasting type. Similarly, in the study conducted by Walia R. et al., 52 (26.8%) cases of CAH were reported, with 42 (21.6%) being simple virilising type and 10 (5.2%) classified as salt-wasting type.[24]

Our study found that 46, XX Disorders of Sex Development (DSD) ranked as the second most prevalent category of DSD, with Congenital Adrenal Hyperplasia (CAH) being the predominant underlying diagnosis. These findings were consistent with those

observed in relevant studies conducted in India and abroad.[8,24,25,28,124] Additionally, we noted that most patients (50%) with CAH exhibited a deficiency in the 21-hydroxylase enzyme, a trend that aligned with findings reported in other studies.[27,125-131] Gupta et al. said that over 90% of CAH cases were associated with 21-hydroxylase deficiency, leading to the accumulation of 17-hydroxyprogesterone (17-OHP), a metabolic by-product before the enzymatic block.[27] In a study conducted by Jaruratanasirikul, CAH emerged as the primary cause of DSD when only patients presenting with genital ambiguity were considered.[131]

Notably, XY DSD males typically exhibit common characteristics as described by AboElella et al., such as hypospadias with or without chordee, bifid scrotum, unilateral or bilateral undescended testis (UDT), and micropenis or macrophallus.[132] Our study revealed that the most common characteristic in XY DSD was proximal hypospadias with or without undescended testis/bifid scrotum, accounting for 55% of the cases. In contrast, Walia et al. reported a higher incidence of disorders related to androgen action (65.7%) but a lower prevalence of hypospadias (8.8%).[24,133] Disorders related to testicular development and bilateral cryptorchidism were observed in 2.5% and 12.5% of our cases, respectively, whereas Walia et al. reported 19.6% and 1.9% rates for these conditions.[24] Significantly, the endocrine profiles of our patients fell within the normal range. Other common clinical findings in XY DSD patients included micropenis, observed in 7.5% of cases.

# STRENGTH AND LIMITATIONS

**Strengths:-**

1. Pioneering Research: The study is the first of its kind in central India, filling a critical knowledge gap.
2. Local Relevance: It directly addresses the healthcare needs of the region.
3. Epidemiological Insight: It contributes to understanding the relative incidence of various DSDs in central India.

**Limitations:-**

1. Genetic Analysis: Lack of genetic analysis due to financial constraints hinders a deeper understanding of DSDs.

# SUMMARY

The AIM of this study,

- To Study the relative incidence of various types of DSDs presenting to AIIMS Bhopal and its comparison with data from other regions
- To study the total incidence of DSDs in the patients being investigated as per existing protocols (positivity rate)
- To study the occurrence of various morphological features in a particular type of DSDs

This study was conducted in the pediatric surgery department, AIIMS Bhopal from Feb 2022 to Aug 2023. A total of 40 patients enrolled, patients who came with hypospadias, with undescended testis, hypospadias with the bifid scrotum, micro penis, bilateral female inguinal hernia, bilateral undescended testis, and clitoromegaly.

The patient’s parents' written consent was taken to participate in the study and to investigate accordingly.

Out of 40 patients, 17 patients came with proximal penile hypospadias, nine patients with hypospadias with UDT, seven patients with bilateral female inguinal hernia, three were bilateral UDT, three were Micropenis, two were mega clitoris and one with bilateral UDT with Micropenis.

We observed that the patients presented with proximal penile hypospadias and UDT have various types of DSDs more frequently steroidal synthesis defects, mixed gonadal dysgenesis, and SRY translocation, followed by Micropenis which can have steroidal synthesis defect and Congenital Adrenal Hyperplasia.

This study shows a 35% positivity rate, with a high incidence of steroidal synthesis defect, followed by Congenital Adrenal Hyperplasia.

This study shows that we must be more vigilant in investigating and proper hormonal workup in patients with a severe variety of proximal penile hypospadias.

# CONCLUSION

This study sheds light on the prevalence of Disorders of Sex Development (DSDs) in central India, offering valuable insights for guiding future research endeavors and establishing diagnostic protocols for such patient populations.

While pediatric clinicians have traditionally adhered to criteria that primarily involve investigating cases of Hypospadias with Undescended Testes (UDT), the findings of this study advocate for adopting a more inclusive approach. Specifically, it recommends lowering the diagnostic threshold, for instance, by considering the evaluation of severe hypospadias cases even in the absence of UDT, as a means to enhance the timely identification of a broader spectrum of DSD patients

# FUTURE SCOPE

This study's findings offer the potential for significant future developments in the field of Disorders of Sex Development (DSDs) in central India. The lowered diagnostic threshold, as recommended, promises the following:

1. Early Detection: Timely identification of DSD cases, improving long-term outcomes.
2. Epidemiological Insights: A more comprehensive understanding of DSD prevalence and distribution.
3. Guideline Standardization: Development of region-specific clinical guidelines.
4. Support Networks: Establishment of patient and family support systems.
5. Genetic Research: Exploring the genetic basis of DSDs for targeted therapies.
6. Quality of Life Assessment: Evaluation of long-term quality of life outcomes.

In summary, this study sets the stage for improved diagnosis, treatment, and support for DSD patients in central India, with potentially far-reaching implications for their well-being and care

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# MASTER CHART

| S.N. | NAME | AGE | SEX | CR UHID | M.N. | DOA | COMPLAINTS | SEX OF REARING | KARYOTYPING | FAMILY HISTORY | Term/Pre Term | Mode of Delivery | indication of LSCS | Birth weight(in kg) | LBW | NICU Admissio | Development History | Height(in cm | stunted | Weight(in kg) | normal/underweight /overweight | B.P. | BP Prediction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Jeevika | 9Y | F | 23212200654802 | 9752140036 | 06-05-2022 | reducible swelling in left inguinal region | FEMALE | 46XX | no similar type of complaints | Pre Term | NVD | NA | 1.8 | YES | YES | Normal according to age | 127 | YES | 20 | UW | 114/78 | Normal |
| 2 | Bhumi Beragi | 12Y | F | 23212200702904 | 7725087894 | 20-05-2022 | reducible swelling both inguinal region | FEMALE | 46XX | no similar type of complaints | Term | NVD | NA | 3.7 | NO | NO | Normal according to age | 150 | NO | 40 | N | 118/68 | Normal |
| 3 | Drasti Dhamnani | 3Y | F | 23212200703874 | 7617371487 | 22-09-2022 | reducible swelling right inguinal region | FEMALE | 46XX | no similar type of complaints | Pre term | LSCS | meconium aspiration | 2.5 | NO | NO | Normal according to age | 102 | NO | 14.48 | N | 90/70 | Normal |
| 4 | shradha goutam | 4y | F | 23212300658082 | 8,27,38,24,181 | 18-04-2023 | reducible swelling in left inguinal region | FEMALE | 46XX | no similar type of complaints | Term | NVD | NA | 2.7 | NO | NO | Normal according to age | 104 | NO | 14.6 | N | 102/68 | Normal |
| 5 | poorvi rajpoot | 4m | F | 23212300456773 | 9817487865 | OPD | megaclitoris | FEMALE | 46XX | no similar type of complaints | Term | NVD | NA | 2.9 | NO | NO | Normal according to age | 53 | NO | 2.8 | UW | 90/50 | Normal |
| 6 | BIO Reena singh | 3D | F | 23212202009263 | 6264441874 | 14-05-2022 | megaclitoris | FEMALE | 46XX | no similar type of complaints | Pre term | LSCS | premature of membrane | 2.6 | NO | NO | delayed | 51 | NO | 2.6 | N | 70/60 | Normal |
| 7 | sharika ahirwar | 3Y | F | 23212301706838 | 9039639511 | OPD | swelling in both inguinal region | FEMALE | 46XX | no similar type of complaints | Term | NVD | NA | 2.5 | NO | NO | Normal according to age | 85 | YES | 10.4 | N | 104/45 | Normal |
| 8 | anshika sahu | 9y | F | 23212202590041 | 9479366133 | 17-01-2023 | reducible swelling in right inguinal region | FEMALE | 46XX | brother have left inguinal hernia | Term | NVD | NA | 2.2 | YES | NO | Normal according to age | 127 | YES | 21 | UW | 111/66 | Normal |
| 9 | ritu malviya | 3y | F | 23212301237609 | 8959762321 | 15-08-2023 | reducible swelling in both inguinal region | FEMALE | 46XX | no similar type of complaints | Term | LSCS | previous LSCS | 2.4 | YES | NO | Normal according to age | 91 | YES | 12.05 | N | 100/97 | Normal |
| 10 | kartik vishwakarma | 2y | M | 23212301690001 | 7440310620 | OPD | bilateral empty scrotum with small penis | MALE | 46XX | no similar type of complaints | Term | NVD | NA | 2.4 | YES | NO | Normal according to age | 86 | NO | 11 | N | 110/78 | Normal |
| 11 | Naman Alani | 12Y | M | 23212200625357 | 8085509595 | OPD | small penis | MALE | 46XY | no similar type of complaints | Term | LSCS | cord encircled neck | 2 | YES | YES | Normal according to age | 144 | NO | 49.8 | OW | 115/72 | Normal |
| 12 | Rudra pratap singh | 5y | M | 23212300142507 | 9827211037 | 23-01-2023 | passing of urine undersurface of penis, empty both scrotum | MALE | 46XY | no similar type of complaints | Pre term | LSCS | previous LSCS | 1.25 | YES | YES | Normal according to age | 110 | NO | 11.92 | N | 96/62 | Normal |
| 13 | Atharv Pathak | 6Y | M | 23212200952625 | 6263968444 | 15-07-2022 | non palpable bil UDT | MALE | 46XY | no similar type of complaints | Term | LSCS | previous LSCS | 1.75 | YES | YES | Normal according to age | 110 | NO | 16.1 | N | 97/63 | Normal |
| 14 | dhruv vishwakarma | 6y | M | 23212201227932 | 9039220462 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.45 | YES | NO | Normal according to age | 122 | NO | 19 | UW | 108/76 | Normal |
| 15 | Durgesh Singh Rajpo | 13Y | M | 23212201521639 | 8120712156 | 13-09-2022 | passing of urine undersurface of penis and left empty scrotum | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.5 | NO | NO | delayed | 138 | YES | 32 | N | 122/86 | Elevated |
| 16 | tanisq | 2.5y | M | 23212201821940 | 9993121747 | OPD | passing of urine undersurface of penis and left empty scrotum | MALE | 46XY | no similar type of complaints | Term | LSCS | narrow pelvis | 2.7 | NO | NO | Normal according to age | 91 | NO | 12.2 | N | 104/60 | Normal |
| 17 | Vivek Pal | 8y | M | 23212201469766 | 9770038191 | 18-10-2022 | passing of urine undersurface of penis,right palpable UDT | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.8 | NO | NO | Normal according to age | 111 | YES | 15.6 | UW | 98/55 | Normal |
| 18 | anuj | 10y | M | 23212202395979 | 9977079519 | 01-02-2023 | passing of urine undersurface of penis and left empty scrotum | MALE | 46XY + m | no similar type of complaints | Pre term | NVD | NA | 1.8 | YES | YES | delayed | 144 | YES | 32.6 | N | 118/76 | Normal |
| 19 | shastra bhargava | 2y | M | 23212200888931 | 8319321772 | 27-06-2022 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 3.75 | NO | NO | Normal according to age | 86 | NO | 10.2 | UW | 96/58 | Normal |
| 20 | Ritik Prajapati | 10yr | M | 23212200158168 | 9896584752 | 29-01-2022 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.5 | NO | NO | Normal according to age | 128 | YES | 23 | N | 108/82 | Normal |
| 21 | Samar Singh | 4yr | M | 23212200148940 | 8717967264 | 21-03-2022 | passing of urine undersurface of penis and left empty scrotum | MALE | 46XX | no similar type of complaints | Pre Term | NVD | NA | 2.7 | NO | NO | Normal according to age | 140 | NO | 14.1 | UW | 112/76 | Normal |
| 22 | Yash Awasthi | 5y | M | 23212200216279 | 7389983532 | 18-04-2022 | passing of urine undersurface of penis, absent left scrotum | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 3.1 | NO | NO | Normal according to age | 118 | NO | 20.4 | N | 114/68 | Elevated |
| 23 | Priyansh Dhurve | 6y | M | 23212200582020 | 9754558587 | OPD | small penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.5 | NO | NO | Normal according to age | 105.5 | YES | 14.3 | UW | 102/64 | Normal |
| 24 | BIO Archna | 5m | M | 23212100124407 | 9754856842 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Pre Term | LSCS | h risk due to fetal comprom | 1.7 | YES | YES | Normal according to age | 60 | NO | 7 | N | 98/62 | Normal |
| 25 | Shivay | 5Y | M | 232122008401 | 9425781545 | 30-04-2022 | non palpable bil UDT | MALE | 46XY | no similar type of complaints | Term | LSCS | delayed labour pain | 2.5 | NO | NO | Normal according to age | 96.5 | YES | 18 | OW | 104/72 | Normal |
| 26 | jayesh kourv | 2y | M | 23212300538991 | 9644656335 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.4 | YES | NO | Normal according to age | 81 | YES | 10 | N | 102/64 | Normal |
| 27 | BIO raj kumari sahu | 2wk | M | 23212202273041 | 9179143212 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Pre term | LSCS | uncontrolled hypertension | 1.57 | YES | YES | delayed | 44 | NO | 1.85 | UW | 70/60 | Normal |
| 28 | jaidev bajpai | 5y | M | 23212201911035 | 9198117260 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.6 | NO | NO | Normal according to age | 98 | YES | 12 | UW | 102/74 | Normal |
| 29 | moh taib | 5y | M | 23212300021009 | 9584323729 | 31-01-2023 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Pre term | NVD | NA | 2.2 | YES | NO | Normal according to age | 103 | NO | 13 | UW | 104/76 | Normal |
| 30 | vishal prajapati | 8y | M | 23212200294501 | 9755415600 | 17-01-2023 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | LSCS | previous LSCS | 4.5 | NO | NO | Normal according to age | 119.5 | NO | 20.3 | N | 106/66 | Normal |
| 31 | BIO ramkishori | 1m | M | 23212300207404 | 9752521511 | 31-01-2023 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Pre term | NVD | NA | 1.4 | YES | YES | delayed | 55 | NO | 2.7 | N | 68/58 | Normal |
| 32 | manas kumar | 6Y | M | 23212300172589 | 9771811684 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.75 | NO | NO | Normal according to age | 114 | NO | 20.7 | N | 120/79 | Elevated |
| 33 | vedansh chouhan | 3y | M | 23212300254402 | 8707397858 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2 | YES | NO | Normal according to age | 100 | NO | 20 | OW | 102/72 | Elevated |
| 34 | raja raghuvanshi | 15y | M | 23212202276171 | 8224892565 | OPD | passing of urine undersurface of penis and left empty scrotum | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.6 | NO | NO | Normal according to age | 163 | NO | 54.9 | N | 127/65 | Normal |
| 35 | dharmendra | 5y | M | 23212301097297 | 9981037622 | OPD | passing of urine undersurface of penis and left empty scrotum | MALE | 46XY | no similar type of complaints | Term | LSCS | previous LSCS | 1.8 | YES | YES | Normal according to age | 87 | YES | 11 | N | 114/72 | Normal |
| 36 | aadarsh yadav | 9y | M | 23212301062361 | 9753972487 | 29-05-2023 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 2.7 | NO | NO | Normal according to age | 128 | NO | 23 | N | 127/70 | Hypertensive |
| 37 | sarthi | 4y | M | 23212201569549 | 8984571515 | OPD | passing of urine undersurface of penis | MALE | 47,XY | no similar type of complaints | Term | NVD | NA | 2.6 | NO | NO | Normal according to age | 105 | NO | 18 | N | 102/62 | Normal |
| 38 | hiyansh panthi | 5y | M | 23212301141229 | 896373927 | OPD | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 3.3 | NO | NO | delayed | 95 | YES | 14 | N | 104/70 | Normal |
| 39 | ram krishna gond | 3y | M | 23212300551571 | 6263481050 | 15-03-2023 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | LSCS | premature of membrane | 1.8 | YES | YES | Normal according to age | 96 | NO | 10.4 | N | 104/76 | Elevated |
| 40 | ved rawat | 2 y | M | 23212202481999 | 7509935755 | 15-02-2023 | passing of urine undersurface of penis | MALE | 46XY | no similar type of complaints | Term | NVD | NA | 1.9 | YES | YES | Normal according to age | 85 | NO | 11.7 | N | 102/74 | Elevated |

| | B.P. | BP Prediction | H.R. | inguinal swelling | genital examination | | | | | | | | | | LAB INVESTIGATIONS | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 114/78 | Normal | 80 | left inguinal swelling | NA | above vaginal opening | NA | NA | NA | NA | normal (appropriate for age) | NA | not palpable | 1 | normal | 135/4.49/102 | NA | NA | NA | NA | NA | NA | NA |
| 4 | 118/88 | Normal | 80 | present | NA | above vaginal opening | NA | NA | NA | NA | normal (appropriate for age) | NA | not palpable | 1 | normal | 134/4.2/103 | NA | NA | NA | NA | NA | NA | NA |
| 5 | 90/70 | Normal | 98 | right inguinal swelling | NA | above vaginal opening | NA | NA | NA | NA | normal (appropriate for age) | NA | not palpable | 1 | normal | 138/4.5/105 | NA | NA | NA | NA | NA | NA | NA |
| 6 | 102/68 | Normal | 80 | left inguinal swelling | NA | above vaginal opening | NA | NA | NA | NA | normal (appropriate for age) | NA | not palpable | 1 | normal | 139/4.3/106 | NA | NA | NA | NA | NA | NA | NA |
| 7 | 80/50 | Normal | 110 | absent | NA | above vaginal opening | NA | NA | NA | NA | 1.5cm | NA | not palpable | 1 | normal | 107/3.68/104 | >200ng/ml | NA | NA | NA | NA | NA | NA |
| 8 | 70/60 | Normal | 120 | absent | NA | single opening in vestibule | NA | NA | NA | NA | 3cm | NA | not palpable | 1 | terior plac | 136/4.12/103 | NA | NA | NA | NA | NA | NA | NA |
| 9 | 104/45 | Normal | 88 | present in both inguinal region | NA | above vaginal opening | NA | NA | NA | NA | normal (appropriate for age) | NA | not palpable | 1 | normal | 139/4.27/108 | NA | NA | NA | NA | NA | NA | NA |
| 10 | 111/66 | Normal | 80 | right inguinal swelling | NA | above vaginal opening | NA | NA | NA | NA | normal (appropriate for age) | NA | not palpable | 1 | normal | 136/3.97/98.5 | NA | NA | NA | NA | NA | NA | NA |
| 11 | 100/97 | Normal | 80 | present in both inguinal region | NA | above vaginal opening | NA | NA | NA | NA | normal (appropriate for age) | NA | not palpable | 1 | normal | 137/4.57/101 | NA | NA | NA | NA | NA | NA | NA |
| 12 | 110/78 | Normal | 76 | absent | NA | tip of phallus | NA | NA | NA | NA | NA | under developed | b/l empty ecrotum | 1 | normal | 137/4.27/103 | >20ng/dl | 4.16 | 0.36 | NA | NA | 20.1 | NA |
| 13 | 115/72 | Normal | 90 | absent | present | tip of phallus | <45 | 3.5 | NO | conical | NA | under developed | present in scrotum | 1 | normal | 134/4.1/102 | NA | 0.19 | 0.51 | NA | NA | 21.0ng/dl | 100.37p |
| 14 | 96/62 | Normal | 120 | absent | present | perineal | >45 | 1.5 | NO | conical | NA | Bifrid Scrotum, | palpable in inguinal canal | 1 | normal | 135/5.1/102 | NA | NA | NA | NA | NA | <7.0ng/dl | 204.2p |
| 15 | 97/63 | Normal | 98 | left inguinal swelling | present | tip of phallus | no | 3 | NO | conical | NA | under developed | not palpable | 1 | normal | 135/4.18/102.84 | NA | NA | NA | NA | NA | NA | NA |
| 16 | 108/76 | Normal | 100 | absent | present | penoscrotal | >45 | 2.6 | NO | conical | NA | normal | present in scrotum | 1 | normal | 132/4.47/107 | NA | NA | NA | NA | NA | 13.69ng/dl | 3.3pg |
| 17 | 122/86 | Elevated | 76 | absent | present | mid penile | <45 | 3.5 | NO | conical | NA | normal | right present in scrotum,left absent | 1 | normal | 133/4.3/105 | NA | NA | NA | NA | NA | 26.80ng/dl | 10.2pg |
| 18 | 104/60 | Normal | 108 | left inguinal swelling | present | mid penile | <45 | 3 | NO | conical | NA | normal | right present in scrotum,left absent | 1 | normal | 131/4.5/102.77 | NA | NA | NA | NA | NA | <7.00ng/dl | 20.2pg |
| 19 | 98/55 | Normal | 86 | right inguinal swelling | present | mid penile | <45 | 2.5 | NO | conical | NA | normal | right inguinal canal,left in scrotum | 1 | normal | 133/4.15/104 | NA | NA | NA | NA | NA | 8ng/dl | 201.2p |
| 20 | 118/76 | Normal | 78 | absent | present | mid penile | >45 | 4 | NO | conical | NA | Bifrid Scrotum, | right inguinal canal,left in scrotum | 1 | normal | 136/4.17/101.04 | NA | NA | NA | NA | NA | 142ng/dl | 62.7p |
| 21 | 96/58 | Normal | 88 | absent | present | penoscrotal | >45 | 2 | YES | conical | NA | normal | present in scrotum | 1 | normal | 134/3.2/103 | NA | NA | NA | NA | NA | 8.6ng/dl | 203.2p |
| 22 | 108/82 | Normal | 80 | present | present | penoscrotal | >45 | 2.5 | NO | conical | NA | normal | inguinal region | 1 | normal | 134/35/102 | NA | NA | NA | NA | NA | 7.6ng/dl | 190pg |
| 23 | 112/76 | Normal | 82 | absent | present | penoscrotal | >45 | 2.5 | NO | conical | NA | >alpable gonad in s | right in scrotum, left absent | 2 | normal | 136/4.13/104 | NA | 2.02mIU | NA | 9.35µg/dl | >23.60ng/m | NA | NE |
| 24 | 114/68 | Elevated | 78 | absent | present | proximal | <45 | 4.5 | NO | conical | NA | underdeveloped | not palpable | 1 | normal | 137/4.20/102 | NA | NA | NA | NA | NA | <7ng/dl | 16.37p |
| 25 | 102/64 | Normal | 82 | absent | present | tip of phallus | <45 | 5 | NO | conical | NA | underdeveloped | present in scrotum | 1 | normal | 138/5.4 | NA | NA | NA | NA | NA | 4.5ng/dl | 1.5pg |
| 26 | 98/62 | Normal | 106 | absent | present | penoscrotal | >45 | 2.5 | NO | flat | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 136/4.2/103 | NA | NA | NA | NA | NA | 41.88ng/dl | 14.0pg |
| 27 | 104/72 | Normal | 80 | absent | present | tip of phallus | no | 5 | NO | conical | NA | normal | not palpable | 1 | normal | 134/4.12/104 | NA | NA | NA | NA | NA | 9ng/dl | 211.2p |
| 28 | 102/64 | Normal | 78 | absent | present | proximal | >45 | 2.5 | NO | conical | NA | normal | present in scrotum | 1 | normal | 144/4.70/104 | NA | NA | NA | NA | NA | 0.19pg/ml | 18.93p |
| 29 | 70/60 | Normal | 82 | absent | present | scrotal | >45 | 2.5 | NO | flat | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 130/5.19/105.8 | NA | NA | NA | NA | NA | <7.00ng/dl | <19.00p |
| 30 | 102/74 | Normal | 80 | absent | present | penoscrotal | >45 | 2.7 | NO | conical | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 135/3.7/103 | NA | NA | NA | NA | NA | <7.0ng/ml | 203.2p |
| 31 | 104/76 | Normal | 80 | absent | present | scrotal | >45 | 1.2 | NO | flat | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 136/4.32/101.89 | NA | NA | NA | NA | NA | <7.00ng/dl | 0.7pg |
| 32 | 106/66 | Normal | 88 | left inguinal swelling | present | penoscrotal | >45 | 3 | NO | conical | NA | Bifrid Scrotum, | right present in the scrotum, left in the inguinal canal | 1 | normal | 133/4.46/101.04 | NA | NA | NA | NA | NA | 12.0ng/dl | 76.26p |
| 33 | 68/58 | Normal | 92 | absent | present | penoscrotal | >45 | 1.5 | NO | conical | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 137/5.8/105 | NA | NA | NA | NA | NA | 332.75ng/dl | 416.22p |
| 34 | 120/79 | Elevated | 110 | absent | present | scrotal | >45 | 1.5 | NO | conical | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 136/3.85/103 | NA | NA | NA | NA | NA | <7.00ng/dl | <17.00p |
| 35 | 102/72 | Elevated | 92 | absent | present | penoscrotal | >45 | 2 | NO | flat | NA | um with both test | present in scrotum | 1 | normal | 137/5.07/106 | NA | NA | NA | NA | NA | <7.00ng/dl | <18.00p |
| 36 | 127/65 | Normal | 86 | left inguinal swelling | operated | perineal | operated | 3.5 | NO | flat | NA | t well developed a | right present in scrotum ,left in inguinal canal | 1 | normal | 135.6/4.17/99.3 | NA | NA | NA | NA | NA | 730ng/dl | 350.46p |
| 37 | 114/72 | Normal | 72 | both side | present | proximal | >45 | 3 | NO | flat | NA | underdeveloped | right hi-lying and left inguinal region | 1 | normal | 137/4.40/107 | NA | NA | NA | NA | NA | 7ng/dl | 1.6pg |
| 38 | 127/70 | Hypertensive | 82 | absent | present | penoscrotal | >45 | 3 | NO | conical | NA | penoscrotal web | present in scrotum | 1 | normal | 139/5.14/106.89 | NA | NA | NA | NA | NA | 10.06ng/dl | 0.2pg |
| 39 | 102/62 | Normal | 80 | absent | present | penoscrotal | >45 | 2.5 | NO | conical | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 134/4.4/104 | NA | NA | NA | NA | NA | 9.6ng/dl | 200.2p |
| 40 | 104/70 | Normal | 76 | absent | present | penoscrotal | no | 2 | NO | conical | NA | normal | present in scrotum | 1 | normal | 135/4.8/105 | NA | NA | NA | NA | NA | 10.0ng/dl | 74.2 |
| 41 | 104/76 | Elevated | 80 | absent | present | penoscrotal | >45 | 2.5 | NO | conical | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 138/4.24/104 | NA | NA | NA | NA | NA | 7ng/dl | 22pg |
| 42 | 102/74 | Elevated | 80 | absent | present | penoscrotal | >45 | 3 | NO | conical | NA | Bifrid Scrotum, | present in scrotum | 1 | normal | 133/4.079/96 | NA | NA | NA | NA | NA | 7ng/dl | 2.2pg |
| 43 | | | | | | | | | | | | | | | | | | | | | | | |

| | | | | LAB INVESTIGATIONS | | | | | | | | Radiology | | | | diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | | | | | | | | | |
| 3 | not palpable | 1 | normal | 135/4.49/102 | NA | NA | NA | NA | NA | NA | NA | <3mm , left indirect inguinal hernia, b/l ovaries and uterus normal app | NA | both inguinal ring open, b/l ingunal hernia | NA | bilateral inguinal hernia |
| 4 | not palpable | 1 | normal | 134/4.2/103 | NA | NA | NA | NA | NA | NA | NA | very 6mm, left overy normal, abdominal wall defect of approx in 2.5 | NA | both inguinal ring open, b/l ingunal hernia | NA | bilateral inguinal hernia |
| 5 | not palpable | 1 | normal | 138/4.5/105 | NA | NA | NA | NA | NA | NA | NA | NA | NA | open right ignuinal canal | NA | bilateral inguinal hernia |
| 6 | not palpable | 1 | normal | 139/4.31/106 | NA | NA | NA | NA | NA | NA | NA | uterus and both ovaries present, infantile | NA | t inguinal hernia, omentum as hernia conte | NA | bilateral inguinal hernia |
| 7 | not palpable | 1 | normal | 107/3.68/104 | >200ng/ml | NA | NA | NA | NA | NA | NA | uterus normal, ovaries not visualised | NA | NA | NA | **Congenital Adrenal Hyperplasia** |
| 8 | not palpable | 1 | terior plac | 136/4.12/103 | NA | NA | NA | NA | NA | NA | NA | ateral gross HDUN with hydrocolpus, no comment on overy and ute | NA | **aparotomy:-** both overy present with uter | NA | cloaca |
| 9 | not palpable | 1 | normal | 139/4.27/108 | NA | NA | NA | NA | NA | NA | NA | ovaries and uterus visualised and size normal according to age | NA | both inguinal ring open, b/l ingunal hernia | NA | bilateral inguinal hernia |
| 10 | not palpable | 1 | normal | 136/3.97/98.5 | NA | NA | NA | NA | NA | NA | NA | uterus and both ovaries present | NA | both side deep inginal ring open | NA | bilateral inguinal hernia |
| 11 | not palpable | 1 | normal | 137/4.57/101 | NA | NA | NA | NA | NA | NA | NA | ovaries and uterus visualised and size normal according to age | NA | both side deep inginal ring open | NA | bilateral inguinal hernia |
| 12 | b/l empty ecrotum | 1 | normal | 137/4.27/103 | >20ng/dl | 4.16 | 0.36 | NA | NA | 20.1 | NA | NA | persistant mullerian structure and non visualisation of testes | NA | NA | NA | **Congenital Adrenal Hyperplasia** |
| 13 | present in scrotum | 1 | normal | 134/4.1/102 | NA | 0.19 | 0.51 | NA | NA | 21.0ng/dl | 100.37pg/ml | 2.1 | rogenous testes, no evidence of any mullerian structure noted, bot | NA | NA | NA | micropenis |
| 14 | palpable in inguinal canal | 1 | normal | 135/5.1/102 | NA | NA | NA | NA | NA | <7.0ng/dl | 204.2pg/ml | 0.34 | NA | NA | NA | NA | b/l UDT with hypospadias |
| 15 | not palpable | 1 | normal | 135/4.18/102.84 | NA | NA | NA | NA | NA | NA | NA | | right testes not visulised in inguinal canal, left testes at left inguinal ca | NA | testes intra abdominal bilateral testes 1.5x0 | uterus with fal | **persistent mullerian duct syndrome** |
| 16 | present in scrotum | 1 | normal | 132/4.47/107 | NA | NA | NA | NA | NA | 13.69ng/dl | 3.3pg/ml | 41 | no evidence of mullerian raminents | NA | NA | NA | **steroidogenesis defects** |
| 17 | right present in scrotum,left absent | 1 | normal | 133/4.3/105 | NA | NA | NA | NA | NA | 26.80ng/dl | 10.2pg/ml | 26.3 | ft scrotal sac is empty, and left testes noted in the left inguinal regio | NA | NA | NA | **steroidogenesis defects** |
| 18 | right present in scrotum,left absent | 1 | normal | 131/4.5/102.77 | NA | NA | NA | NA | NA | <7.00ng/dl | 20.2pg/ml | 3.5 | left testes at superficial inguinal region | NA | NA | NA | left palpable UDT with hypospadias |
| 19 | right inguinal canal,left in scrotum | 1 | normal | 133/4.15/104 | NA | NA | NA | NA | NA | 8ng/dl | 201.2pg/ml | 0.39 | ectopic crossed fused left kidney with cystic dysplastic changes | NA | NA | NA | hypospadias with UDT |
| 20 | right inguinal canal,left in scrotum | 1 | normal | 136/4.17/101.04 | NA | NA | NA | NA | NA | 142ng/dl | 62.7pgml | 22 | NA | NA | NA | streak gonad | **mixed gonadal dysgenesis** |
| 21 | present in scrotum | 1 | normal | 134/3.2/103 | NA | NA | NA | NA | NA | 8.6ng/dl | 203.2pg/ml | 0.42 | NA | NA | YA | NA | proximal penile hypospadias |
| 22 | inguinal region | 1 | normal | 134/35/102 | NA | NA | NA | NA | NA | 7.6ng/dl | 190pg/dl | 0.4 | NA | NA | NA | NA | PPH with left palpable UDT |
| 23 | right in scrotum, left absent | 2 | normal | 136/4.13/104 | NA | 2.02mIU | NA | 9.35µg/dl | >23.60ng/m | NA | NB | NA | NA | NA | in right side, left testis close to right Deep i | NA | **SRY translocation** |
| 24 | not palpable | 1 | normal | 137/4.20/102 | NA | NA | NA | NA | NA | <7ng/dl | 16.37pg/ml | 4.29 | no mullerian structure | nullerian sturuc | absent right testis,left testes intra-abdomin | NA | bilateral non palbpe UDT |
| 25 | present in scrotum | 1 | normal | 138/5.4 | NA | NA | NA | NA | NA | 4.5ng/dl | 1.5pg/ml | 30.6 | NA | NA | NA | NA | **steroidogenesis defects** |
| 26 | present in scrotum | 1 | normal | 136/4.2/103 | NA | NA | NA | NA | NA | 41.88ng/dl | 14.0pg/ml | 24.6 | B/L testes in scrotal sac | NA | NA | NA | **steroidogenesis defects** |
| 27 | not palpable | 1 | normal | 134/4.12/104 | NA | NA | NA | NA | NA | 9ng/dl | 211.2pg/ml | 0.42 | NA | NA | NA | NA | bilateral non palbpe UDT |
| 28 | present in scrotum | 1 | normal | 144/4.70/104 | NA | NA | NA | NA | NA | 0.19pg/ml | 18.93pg/ml | 0.01 | NA | NA | NA | NA | proximal penile hypospadias |
| 29 | present in scrotum | 1 | normal | 130/5.19/105.8 | NA | NA | NA | NA | NA | <7.00ng/dl | <19.00pg/ml | 3.68 | no mullerian structure | NA | NA | NA | proximal penile hypospadias |
| 30 | present in scrotum | 1 | normal | 135/3.7/103 | NA | NA | NA | NA | NA | <7.0ng/ml | 203.2pg/ml | 0.34 | NA | NA | NA | NA | proximal penile hypospadias |
| 31 | present in scrotum | 1 | normal | 136/4.32/101.89 | NA | NA | NA | NA | NA | <7.00ng/dl | 0.7pg/ml | 100 | NA | NA | NA | NA | **steroidogenesis defects** |
| 32 | right present in the scrotum, left in the inguinal canal | 1 | normal | 133/4.46/101.04 | NA | NA | NA | NA | NA | 12.0ng/dl | 76.26pg/ml | 1.5 | NA | NA | NA | NA | penoscrotal transposition |
| 33 | present in scrotum | 1 | normal | 137/5.8/105 | NA | NA | NA | NA | NA | 332.75ng/dl | 416.22pg/ml | 8 | NA | NA | NA | NA | roximal penile hypospadias with penoscrotal transposition |
| 34 | present in scrotum | 1 | normal | 136/3.85/103 | NA | NA | NA | NA | NA | <7.00ng/dl | <17.00pg/ml | 4.11 | no mullerian structure | NA | NA | NA | roximal penile hypospadias with penoscrotal transposition |
| 35 | present in scrotum | 1 | normal | 137/5.07/106 | NA | NA | NA | NA | NA | <7.00ng/dl | <18.00pg/ml | 3.8 | no mullerial structure | NA | NA | NA | proximal penile hypospadias |
| 36 | right present in scrotum ,left in inguinal canal | 1 | normal | 135.6/4.17/99.3 | NA | NA | NA | NA | NA | 730ng/dl | 350.46pg/ml | 20.86 | no mullerial structure | NA | penoscrotal hypospadias with left UDT | NA | **steroidogenesis defects** |
| 37 | right hi-lying and left inguinal region | 1 | normal | 137/4.40/107 | NA | NA | NA | NA | NA | 7ng/dl | 1.6pg/ml | 43.7 | no mullerial structure | NA | NA | NA | **steroidogenesis defects** |
| 38 | present in scrotum | 1 | normal | 139/5.14/106.89 | NA | NA | NA | NA | NA | 10.06ng/dl | 0.2pg/ml | 503 | no mullerial structure | NA | NA | NA | **steroidogenesis defects** |
| 39 | present in scrotum | 1 | normal | 134/4.4/104 | NA | NA | NA | NA | NA | 9.6ng/dl | 200.2pg/ml | 0.48 | NA | NA | NA | NA | proximal penile hypospadias |
| 40 | present in scrotum | 1 | normal | 135/4.8/105 | NA | NA | NA | NA | NA | 10.0ng/dl | 74.26 | 1.34 | NA | NA | NA | NA | proximal penile hypospadias |
| 41 | present in scrotum | 1 | normal | 138/4.24/104 | NA | NA | NA | NA | NA | 7ng/dl | 22pg/ml | 3.18 | NA | NA | NA | NA | proximal penile hypospadias |
| 42 | present in scrotum | 1 | normal | 133/4079/96 | NA | NA | NA | NA | NA | 7ng/dl | 2.2pg/ml | 31.81 | NA | NA | NA | NA | **steroidogenesis defects** |
| 43 | | | | | | | | | | | | | | | | | |

**NOTE:- Further investigation and evaluation be planned later/not applicable.**

# ANNEXURE-1

# DATA SHEET

## Clinico-Epidemiological Profile of Disorders of Sex Development Presenting to a Tertiary Care Centre

**PATIENT PARTICULARS:-**

NAME:-

AGE:- SEX:-

ADDRESS:-

UHID:-

MOB. NO. -

DATE OF ADMISSION:-

CHIEF COMPLAINTS:-

HISTORY OF PRESENT ILLNESS:- sex of rearing

FAMILY HISTORY:- H/O of similar complaints or unexplained deaths in siblings history of ovarian tumor and any history of treatment for infertility in both parents.

ANTENATAL HISTORY:-

- Gravid / para / live birth
- Maternal age during pregnancy
- History of drug intake for pregnancy
- History of drug intake during pregnancy
- History of hospitalization
- History of maternal virilisation
- Antenatal ultrasound

BIRTH HISTORY:-

- Full term / preterm
- Mode of delivery - NVD/LSCS
- If LSCS-cause for LSCS
- Birth weight – history of IUGR

- History of admission in NICU

DEVELOPMENT HISTORY:-

PERSONAL HISTORY:-

Treatment history – Medical and Surgical

General examination-- abnormal facies, pigmentation, secondary sexual characters – pubic and axillary hair, breast development/ gynecomastia

Height_____ weight _____

Temperature_____, HR_____, BP___/___

**LOCAL EXAMINATION:-**

**Inguinal region** – swelling____contents_____

**Phallus: –**

**Penis:** – SPL____ / circumference__ / diameter __/ penile torsion / raphae

**Dorsal hood** :- present/absent and adequate (thickness and well spread)

**Meatus** - opening site- tip of phallus/ distal/ mid/ proximal/ penoscrotal/ scrotal/ perineal, size of the meatus

**Urethral plate** - well developed/ skin lined/ mucosa lined

**Glans** – shape-conical / flat, glandular groove - deep/ shallow

**Chordee**- $<45^0$, $> 45^0$/ glandular tilt

**Clitoris-** length_____ , width_____

**Scrotum-** bifid /normal, testicular impression, pigmentation, rugosity, penoscrotal web

**Labio-scrotal folds:-** pigmentation and rugosity, posterior fusion

**Gonads:-** present in scrotum/ inguinal region/ ectopic site/ absent

**Number of orifices in perineum:-** the location of the orifices

**Anus: –** position, patency, anogenital distance, palpation of the uterus through rectal examination

**Investigations:**

1. **LABORATORY**

Serum electrolytes Na____,K_____Cl_____

Serum glucose

SRY/X chromosome

17 hydroxyprogesterone

Cortisol

ACTH

Luteinizing hormone (LH)

Follicular stimulating hormone (FSH)

Serum testosterone

Dihydroxy testosterone

Anti-Mullerian hormone

Karyotyping

2. **RADIOLOGY**

Ultrasonography (USG)

Magnetic resonance imaging (MRI)

Genitogram

**3. SURGICAL**

Cysto-urethroscopy

Laparoscopy

Gonadal biopsy-histology, cytogenetic,molecular analysis

# ANNEXURE-2

## INFORMED CONSENT

**Title of the study:-**"Clinico-epidemiological profile of disorders of sex development presenting to a tertiary care center"

You have been informed about the study by Dr. Sujeet Kumar, SR Pediatric Surgery, AIIMS, Bhopal, whom you can contact at any time if you have any queries regarding the research study.

| | Yes/No |
|---|---|
| 1. I confirm that I have read and understood the information sheet for the study. I confirm that the study has been explained to me and I have had ample time and opportunity to ask the questions. | [ ] |
| 2. I understand that participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. | [ ] |
| 3. I agree not to restrict the use of any data or result that arises from this study provided such use is only for the scientific purpose(s) | [ ] |

To be filled by the person taking the consent:- I hereby confirm that I have fully explained all the aspects of the study to the parents/ guardians/ legally acceptable representative of the subject.

Sign of the person conducting the informed consent……..

Sign of the study investigator: Dr.Sujeet Kumar…….

Date ……..

To be filled by parent/ guardian:

Name of the patient……..

Name of Guardian/ Parents……..

Relationship with the patient:…….

Sign of Guardian/Parents……..

## सूचित सहमति

अध्ययन का शीर्षक-:"एक तृतीयक चिकित्सा केंद्र में लिंग विकास के विकारों के लाक्षणिक एवं जानपदिक विवरण का अध्ययन"

डॉ .सुजीत कुमार, सीनियर रेजिडेंट पीडियाट्रिक सर्जरी, एम्स, भोपाल द्वारा आपको अध्ययन के बारे में सूचित किया गया है कि यदि आप शोध अध्ययन के संबंध में कोई प्रश्न पूछना चाहते हैं तो आप किसी भी समय संपर्क कर सकते हैं।

| | [हां/नहीं[ |
|---|---|
| मैं पुष्टि करता /करती हूं कि मैंने अध्ययन के लिए सूचना पत्रक को पढ़ और समझ लिया है।मैं पुष्टि करता हूं कि मुझे अध्ययन के बारे में बता दिया गया हैऔर मेरे पास प्रश्न पूछने का पर्याप्त समय और अवसर है। | |
| मैं समझता हूं कि अध्ययन में भाग लेना स्वैच्छिक है और मैं बिना किसी कारण बताए, मेरी चिकित्सा देखभाल या कानूनी अधिकारों को प्रभावित किए बिना किसी भी समय वापस लेने के लिए स्वतंत्र हूं। | |
| मैं सहमत हूं कि इस अध्ययन से उत्पन्न होने वाले किसी भी डेटा या परिणाम के उपयोग को प्रतिबंधित नहीं किया जाएगा , बशर्ते ऐसा उपयोग केवल वैज्ञानिक उद्देश्यों के लिए हो | |

सहमति लेने वाले व्यक्ति द्वारा भरा जाना:-

मैं एतद्द्वारा पुष्टि करता हूं कि मुझे अध्ययन के सभी पहलुओं के बारे में माता-पिता /अभिभावकों/ विषय के कानूनी रूप से स्वीकार्य प्रतिनिधि को पूरी तरह से समझाया गया है।

सूचित सहमति का संचालन करने वाले व्यक्ति का

हस्ताक्षर.....:.....

अध्ययन अन्वेषक के हस्ताक्षर:-

डॉ .सुजीत कुमार…….....

दिनांक……..…..

माता-पिता/अभिभावक द्वारा भरा जाना है:

रोगी का

नाम……..……

……

अभिभावक/माता-पिता का

नाम……..…….……

…… ..

रोगी के साथ

संबंध:……

……

अभिभावक/माता-पिता के

हस्ताक्षर……..……

……

# ANNEXURE-3

## PARTICIPANT INFORMATION SHEET

Dear Parent/Guardian of ……..

We are conducting a retrospective as well as prospective observational study at All India Institute of Medical Sciences, Bhopal to study the **Clinico-epidemiological profile of Disorders of Sex Development presenting to a tertiary care centre**. You are requested to go through the following paragraphs:-

i. **Title :-** Clinico-epidemiological profile of disorders of sex development presenting to a tertiary care centre-an observational study

ii. **Purpose of the study:-**to find out the incidence and pattern of disorder of sex development in central India and overall burden of disease in theregion.

iii. **What are we going to do: -**We will be reviewing the treatment charts.laboratory& radiological records of the subjects included in the study. No change in the management has been planned.

iv. **Any risk to subject associated with the study:-minimal risk due to breach in confidentiality.**

v. **Confidentiality:-**all the records will be confidential, and the patient identity would be known to the chief investigator and would not be released to anybody else.

vi. **Provision of free treatment for research related injury: -**no research related injury is expected as there is no deviation from standard management for disorder of sex development.

vii. **Freedom of individual to participate and to withdraw from research at any time without penalty or loss of benefits to which the subject would otherwise entitled:-**participation in the study is voluntary. Refusal to participate will not influence care of the participants in this hospital in any way.

viii. **Cost and source of investigations and drugs:-**You will not bechargedanything extrafor this study.

ix. **Available information sources:-**the study is approved by the Ethical Review Board AIIMS, Bhopal.

   a. In case of any concern or questions about the study, please contact the study investigator: Dr. Sujeet Kumar, Senior Resident, Department of Pediatric Surgery, AIIMS, Bhopal. M.N.9752907096, Email-Id: pandresujeet006@gmail.com

b. In case of any concerns about the conduct of this research study, please contact the AIIMS Human .Ethics Committee: Dr. Shashank Purwar, Member Secretary, IHEC-PGR, AIIMS Bhopal. Contact N.07773010099, Email id: ihecpgr@aiimsbhopal.edu.in

## प्रतिभागी सूचना पत्र

प्रिय……..माता-पिता/अभिभावक

हम अखिल भारतीय आयुर्विज्ञान संस्थान, भोपाल में एक तृतीयक चिकित्सा केंद्र में लिंग विकास के विकारों के लाक्षणिक एवं जानपदिक विवरण का अध्ययन करने के लिए एक पूर्वव्यापी और साथ ही भावी अवलोकन अध्ययन कर रहे हैं।आप से अनुरोध है कि निम्नलिखित अनुच्छेदों को पढ़ें: -

शीर्षक -:'एक तृतीयक चिकित्सा केंद्र में लिंग विकास के विकारों के लाक्षणिक एवं जानपदिक विवरण का अध्ययन"

मध्य भारत में यौन विकास के विकार की घटनाओं और पैटर्न का पता लगाने और वहां बीमारी के समग्र बोझ का पता लगाने के लिए

हम क्या करेंगे -:हम अध्ययन में शामिल विषयों के नैदानिक, रेडियोलॉजी एवं जॉचों के दस्तावेज का अवलोकन एवं अध्ययन करेंगे, मरीज के इलाज में कोई भी परिवर्तन प्रस्तावित नहीं है।

अध्ययन से जुड़े विषय के लिए कोई जोखिम - :**गोपनीयता भंग होने के कारण न्यूनतम जोखिम की संभावना है।**

गोपनीयता :सभी रिकॉर्ड गोपनीय होंगे, और रोगी की पहचान मुख्य अन्वेषक को पता चल जाएगी और किसी और को जारी नहीं की जाएगी।

अनुसंधान संबंधी चोट के लिए नि:शुल्क उपचार का प्रावधान -: अनुसंधान से संबंधित चोट की कोई उम्मीद नहीं है क्योंकि यौन विकास के विकार के लिए मानक प्रबंधन से कोई विचलन नहीं है।

व्यक्ति को किसी भी समय बिना किसी दंड या लाभों की हानि के भाग लेने और अनुसंधान से हटने की स्वतंत्रता जिसके लिए विषय अन्यथा हकदार होगा - :अध्ययन में भाग लेना स्वैच्छिक है।भाग लेने से इनकार करने से इस अस्पताल में प्रतिभागियों की देखभाल किसी भी तरह से प्रभावित नहीं होगी।

जांच और दवाओं की लागत और स्रोत -:इस अध्ययन परियोजना से संबंधित किसी अन्य चीज के लिए आपसे कोई शुल्क नहीं लिया जाएगा।

उपलब्ध सूचना स्रोत -:अध्ययन को एथिकल रिव्यू बोर्ड एम्स, भोपाल द्वारा अनुमोदित किया गया है।

अध्ययन के बारे में किसी भी चिंता या प्रश्न के मामले में, कृपया अध्ययन अन्वेषक से संपर्क करें : डॉ सुजीत कुमार, वरिष्ठ निवासी, बाल शल्य चिकित्सा विभाग, एम्स, भोपाल।एम.एन. 9752907096, ईमेल-आईडी :pandresujeet006@gmail.com

इस शोध अध्ययन के संचालन के बारे में किसी भी चिंता के मामले में, कृपया एम्स मानव आचार समिति से संपर्क करें :डॉ शशांक पुरवार, सदस्य सचिव, आईएचईसीपीजीआर, एम्स भोपाल।संपर्क न0. 7773000869, ईमेल आईडी :ihecpgr@aiimsbhopal.edu.in

# ANNEXURE-4

## ASSENT FORM

Dear participant

We are doing a study on "**Clinico-epidemiological profile of disorders of sex development presenting to a tertiary care centre**"

We are asking you for registering in this study as this will help us to identify the incidence of the disease and which type of disorder of sex development is prevalent in this region.

You can ask questions about this study at any time. If you decide at any time not to participate, you can ask us to stop.

If you sign this paper, it means that you have read this and that you want to be in the study.

If you don't want to be the part of this study then please donot sign this paper. Being in the study is up to you, and no one will be upset if you donot sign this paper or if change your mind later.

Your signature:……

Date: ……..

Your name:……..

Signature of the person obtaining the consent:-…….

Name :-……

Date:-……

# अनुमति प्रपत्र

प्रिय प्रतिभागी

हम एक तृतीयक चिकित्सा केंद्र में लिंग विकास के विकारों के लाक्षणिक एवं जानपदिक विवरण का अध्ययन पर एक अध्ययन कर रहे हैं।

हम आप से इस अध्ययन में पंजीकरण करने के लिए कह रहे हैं क्योंकि इस से हमें बीमारी की घटनाओं की पहचान करने में मदद मिलेगी और उस क्षेत्र में किस प्रकार का यौनविकास विकार प्रचलित है।

आप इस अध्ययन के बारे में किसी भी समय प्रश्न पूछ सकते हैं।यदिआप किसी भी समय भाग न लेने का निर्णय लेते हैं, तो आप हमें रुकने के लिए कह सकते हैं।

यदि आप इस पेपर पर हस्ताक्षर करते हैं, तो इसका मतलब है कि आपने इसे पढ़ लिया है और आप अध्ययन में शामिल होना चाहते हैं।

यदि आप अध्ययन नहीं बनना चाहते हैं, तो इस प्रपत्र पर हस्ताक्षर न करें।अध्ययन में रहना आप पर निर्भर है, और यदि आप इस पेपर पर हस्ताक्षर नहीं करते हैं या बाद में अपना विचार बदलते हैं तो कोई भी परेशान नहीं होगा।

आपके हस्ताक्षर:.....

दिनांक:.....

आपके नाम:.....

सहमति प्राप्त करने वाले व्यक्ति के हस्ताक्षर-:.....

नाम-: .....

दिनांक-:.....**....**